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RESEARCH NEWS AND VIEWS FROM ELSEVIER

Tissue factor and inflammatory cytokines may play a role in chronic thromboembolic pulmonary hypertension

Tissue factor gene expression has been shown to be increased in patients with chronic thromboembolic pulmonary hypertension. ▸3

More stories from CHEST 2016 inside! See page 10.

Pulmonary artery pressure-guided heart failure management reduces 30-day readmissions

Circ Heart Fail

Pulmonary artery pressure-guided HF management in US Medicare-eligible patients led to a 49% reduction in total HF hospitalisations and a 58% reduction in all-cause 30-day readmissions. ▸3

Rare mutation in ASGR1 is associated with a reduced risk of CAD

N Engl J Med

Less is more when it comes to the activity of the asialoglycoprotein receptor (ASGR1). ASGR1 haploinsufficiency was associated with reduced levels of non-HDL cholesterol and a reduced risk of coronary artery disease. ▸6

Novel method for earlier detection of phrenic nerve injury during cryoballoon ablation

Heart Rhythm

Recovery from PNP improved from months to hours post-operatively by utilising an improved method of pacing with the minimum output. ▸8

Increased incidence of ventricular arrhythmias in patients with advanced cancer and ICDs

JACC Clin Electrophysiol

One-third of patients who had received ICDs developed ventricular arrhythmia after a diagnosis of cancer. The incidence was significantly higher in those with advanced metastatic disease. ▸14

OPINION

"Practice trumps theory, and pursuit of "hard" clinical endpoints should and must remain the bedrock of informing our interventions to manage patients' cardiovascular risk

Dr Peter Libby ▸4

MYOCARDIAL DISEASE

Global LGE on CMR is a helpful prognostic indicator in patients with AL cardiac amyloidosis. ▸5

CORONARY HEART DISEASE

"This is an exciting period for imaging in cardiovascular disease, and T1 mapping continues to generate much enthusiasm as a developing technique with the potential for having substantial clinical impact on diagnosis and management strategies. ▸6

CONFERENCE

CHEST

A gas-driven pump is used to deliver prostacycline in patients with severe PHTN ▸10

Long-term mechanical ventilation is effective in children with PHTN ▸11

Balloon pulmonary angioplasty reduces mean pulmonary arterial pressure to ≤30 mmHg ▸12

INTERVENTIONAL CARDIOLOGY

Not only does guideline-based therapy for acute myocardial infarction improve 30-day survival, it also results in a sustained benefit in survival that can be observed as far out as 17 years. ▸15

NEW LOOK • NEW NAME
MORE EXPERT OPINION
MORE JOURNAL ARTICLE REVIEWS
MORE CONFERENCE COVERAGE NEWS

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Tissue factor and inflammatory cytokines may play a role in chronic thromboembolic pulmonary hypertension

Continued from page 1.

Thrombosis and inflammation are two major factors underlying chronic thromboembolic pulmonary hypertension, says Dr Minxia Yang, MD, of the First Affiliated Hospital of Fujian Medical University, Fuzhou, China.

Tissue factor, C-reactive protein, tumour necrosis factor α, and monocyte chemoattractant protein 1 may play critical roles in the process of chronic thromboembolic pulmonary hypertension thrombosis and pulmonary vascular remodelling.

Dr Yang and colleagues enrolled 10 patients with a confirmed diagnosis of chronic thromboembolic pulmonary hypertension, 20 with pulmonary thromboembolism, and 15 with other types of pulmonary hypertension, along with 20 healthy control subjects.

The immunoturbidimetric method was used to determine the plasma content of C-reactive protein. Plasma levels of tumour necrosis factor α, monocyte chemoattractant protein 1, and tissue factor antigen were measured by enzyme-linked immunosorbent assay. Tissue factor activity was measured by the chromogenic substrate method. Percoll density gradient centrifugation was used to separate peripheral blood mononuclear cells from plasma.

The level of monocyte tissue factor mRNA was examined by reverse transcriptase polymerase chain reaction. Correlations between these indices above were analysed.

In patients with chronic thromboembolic pulmonary hypertension, expression of C-reactive protein, tumour necrosis factor α, and monocyte chemoattractant protein 1 was significantly higher than in controls.

> "Tissue factor gene expression was shown to be increased in patients with chronic thromboembolic pulmonary hypertension, suggesting that blood-borne tissue factor mainly comes from mononuclear cells

Levels of tissue factor activity, tissue factor antigen, and tissue factor mRNA in monocyte cells were increased in patients with chronic thromboembolic pulmonary hypertension vs control subjects. Only tissue factor antigen and tissue factor mRNA levels differed significantly.

In patients with chronic thromboembolic pulmonary hypertension, levels of C-reactive protein, monocyte chemoattractant protein 1, and tumour necrosis factor α correlated significantly with the level of tissue factor antigen in plasma.

Dr Yang concluded that tissue factor gene expression was shown to be increased in patients with chronic thromboembolic pulmonary hypertension, suggesting that blood-borne tissue factor mainly comes from mononuclear cells. Tissue factor expression correlated significantly with levels of C-reactive protein, tumour necrosis factor α, and monocyte chemoattractant protein 1. These factors may play an important role in the development of chronic thromboembolic pulmonary hypertension via the inflammation-coagulation-thrombosis cycle.

The increase in tissue factor expression in the plasma of patients with chronic thromboembolic pulmonary hypertension, partly due to an increase in monocyte tissue factor mRNA levels. Monocyte tissue factor plays a key role during the process of chronic thromboembolic pulmonary hypertension thrombosis.

At the same time, the inflammatory factors C-reactive protein, tumour necrosis factor α, and monocyte chemoattractant protein 1 increased in the plasma of patients with chronic thromboembolic pulmonary hypertension and correlated with mean pulmonary artery pressure, indicating that they are involved in the pathogenesis of chronic thromboembolic pulmonary hypertension and determine disease severity.

Moreover, high expression of tissue factor correlated with expression of the inflammatory factors C-reactive protein, tumour necrosis factor α, and monocyte chemoattractant protein 1 in patients with chronic thromboembolic pulmonary hypertension.

Tissue factor, C-reactive protein, tumour necrosis factor α, and monocyte chemoattractant protein 1 may not be attractive molecules to use in screening for chronic thromboembolic pulmonary hypertension. These factors may, however, hold value in determining prognosis. The prognostic value of tissue factor, C-reactive protein, tumour necrosis factor α, and monocyte chemoattractant protein 1 was not evaluated in this study. ■

Editor's pick

JOURNAL SCAN

Heart failure management guided by pulmonary artery pressure reduces 30-day readmissions

Circulation: Heart Failure

Take-home message

- This was a randomised study of 245 US Medicare-eligible and compliant participants from the CHAMPION trial. A permanent cardiac micro-electromechanical system (MEMS)–based pressure sensor was implanted in the pulmonary artery, and the impact of heart failure care guided by pulmonary artery pressure on 30-day readmissions was assessed. Medication changes in the treatment group were based on uploaded pressures made available to investigators, whereas, in the control group, changes were based on symptoms and daily weights. In the 515-day post-implant follow-up, significant decreases were observed for the overall rate of heart failure hospitalisations (49%; P < 0.0001) and all-cause 30-day readmissions (58%; P = 0.0080) in the treatment group compared with the control group.
- Reductions in the overall rate of hospitalisations and all-cause 30-day readmissions occurred in individuals who underwent pulmonary artery pressure–guided treatment for heart failure.

Dr Douglas L Mann

The CHAMPION trial was a landmark randomised controlled single-blind study of 550 patients with NYHA class III heart failure (HF) who had a HF hospitalisation within the prior year. All patients in the CHAMPION trial underwent implantation of a proprietary ambulatory pulmonary artery (PA) pressure monitoring system (CardioMEMS™) and were then randomised to the active monitoring group (PA pressure-guided HF management on top of standard of care) or to the blind therapy group (HF management by standard clinical assessment) and followed for a minimum of 6 months. The CHAMPION trial showed that adjusting medical therapy based on PA pressures resulted in improved clinical outcomes in patients with both HFrEF and HFpEF. To determine whether the PA pressure-guided HF management was effective in a subset of Medicare-eligible patients in the CHAMPION trial, Adamson and colleagues conducted a retrospective analysis of the HF admissions over 13 months of follow-up in patients >65 years of age at the time of PA catheter insertion.

Adamson et al showed that there was an approximate 50% reduction in overall HF hospitalisations and an approximate 60% decrease in 30-day readmission rates in the treatment group. Given that the Medicare-eligible patients represented approximately 45% of patients enrolled in CHAMPION, the results of this non-prespecified retrospective analysis are not that surprising, insofar as the primary results of the entire follow-up period (mean 15 ± 7 months) for all of the patients in the CHAMPION trial showed that there was an approximate 40% decrease in HF-related hospitalisations. What is new in the most recent analysis by Adamson is the reduction in 30-day readmission rates in the Medicare-eligible patients who received PA pressure-guided HF management. Given that the Hospital Readmissions Reduction Program requires CMS to reduce payments to hospitals with excess readmissions for HF within 30 days, this finding is potentially very important. The authors also state that one of the compelling reasons to perform the subset analysis on Medicare-eligible patients is that older patients "stereotypically" don't interact well with technologies and are under-represented in clinical trials.

This argument is specious for two reasons. First, the inclusion criteria for the CHAMPION protocol allowed for enrolling Medicare-eligible patients, so the CHAMPION investigators had to have made a prior assumption that this population would be tech-savvy enough to interface with the PA-catheter monitoring device in order to be enrolled in the treatment arm of the trial. Second, the incidence of HF increases as a function of increasing age; accordingly, Medicare-eligible patients are exactly the types of patients who one would want to enrol in HF trials. Indeed, the mean age of the NYHA class II–IV HFrEF patients enrolled in the recent PARADIGM trial, which led to the rapid US FDA approval of ENTRESTO (LCZ696), was 63 ± 7 years.

In summary, the interesting post hoc analysis of the CHAMPION trial by Adamson and colleagues does add incrementally to our knowledge regarding the importance of monitoring intracardiac PA pressures, especially with respect to demonstrating decreased 30-day HF rehospitalisation. Given the current pressures on cost containment in healthcare systems, one would hope that the authors will also perform a future economic analysis on the overall impact of monitoring PA pressure on Medicare reimbursement for HF patients in order to better determine whether the cost of implanting the CardioMEMS device is offset by the cost savings from preventing hospitalisations, which is the question that we need to ask as well.

Abstract

BACKGROUND This study examines the impact of pulmonary artery pressure-guided heart failure (HF) care on 30-day readmissions in Medicare-eligible patients.

METHODS AND RESULTS The CardioMicroelectromechanical system (CardioMEMS) Heart Sensor Allows Monitoring of Pressures to Improve Outcomes in New York Heart Association Class III Heart Failure Patients (CHAMPION) Trial included 550 patients implanted with a permanent MEMS-based pressure sensor in the pulmonary artery. Subjects were randomised to a treatment group (uploaded pressures were made available to investigators) or a control group (uploaded pressures were not made available to investigators). This analysis focuses on the 245 Medicare-eligible subjects for whom compliance with daily transmissions was 93% compared with 88% for the overall population. Medications were changed more often in the treatment group using pressure information compared with the control group using symptoms and daily weights alone. During the 515 days follow-up after implant, the overall rate of HF hospitalisations was 49% lower in the treatment group (60 HF hospitalisations, 0.34 events/patient-year) compared with control (117 HF hospitalisations, 0.67 events/patient-year; hazard ratio 0.51, 95% confidence interval 0.37–0.70; P < 0.0001). Of the 177 HF hospitalisations, 155 qualified as an index HF hospitalisation. All-cause 30-day readmissions were 58% lower in the treatment group (0.07 events/patient-year) compared with 0.18 events/patient-year in the control group (hazard ratio 0.42, 95% confidence interval 0.22–0.80; P = 0.0080).

CONCLUSIONS Pulmonary artery pressure-guided HF management in Medicare-eligible patients led to a 49% reduction in total HF hospitalisations and a 58% reduction in all-cause 30-day readmissions.

Pulmonary artery pressure-guided heart failure management reduces 30-day readmissions Circ *Heart Fail* 2016;9:e002600, PB Adamson, WT Abraham, LW Stevenson, et al.

EXPERT OPINION

Another crack in the HDL edifice

BY DR PETER LIBBY

Recent data have shoved the "HDL hypothesis" to the ropes. High-density lipoprotein cholesterol (HDL-C) concentrations in plasma indubitably and consistently correlate inversely with cardiovascular events in observational studies. Yet, strong human genetic data that have emerged from recent analyses cast serious doubt on the causality of HDL-C as a protective factor against cardiovascular events in humans. Moreover, multiple pharmacologic manipulations that raise HDL-C have failed to reduce cardiovascular events in superbly conducted large-scale clinical endpoint trials. Agents that raise HDL, but that fail to reduce cardiovascular events in such trials, include fibric acid derivatives (fenofibrate; ACCORD), nicotinic acid (AIM-HIGH and HPS-2/THRIVE), and all three inhibitors of cholesteryl ester transfer protein (CETP) for which we have outcome data. At present, the most recent disappointment, communicated by Eli Lilly on October 12, 2015, informed the community of the halting of a large cardiovascular outcomes trial with the CETP inhibitor evacetrapib for apparent futility. Merck announced on November 13, 2015, that it was continuing the outcome study with a fourth CETP inhibitor, anacetrapib.

The field of clinical lipidology has struggled to come to terms with the paradox of an enormous preclinical and epidemiologic database suggesting that raising HDL should reduce cardiovascular events in face of the consistent failure of such strategies in well-powered and well-performed outcome trials. Given the consistency and magnitude of the observational and in vitro mechanistic database, many have argued that HDL-C does not capture the biological functions of HDL species or the properties of particular subclasses of these particles. HDL shows considerable heterogeneity in both structure and function. In particular, "nascent" relatively cholesterol-poor particles known as "pre-beta HDL" may function to siphon cholesterol from cells more effectively than other classes of HDL. Thus, the subpopulation of pre-beta HDL, rather than total HDL-C, might reflect better the ability to function in "reverse cholesterol transport," removing cholesterol from macrophages, a cell type that when loaded with cholesterol may contribute to the mischief of atherogenesis and the clinical complications of this disease. Hence, the ability to measure HDL subclasses, and more importantly their ability to function in reverse cholesterol transport, has garnered enormous interest.

In vitro assays can indeed assess the ability of HDL to remove cholesterol from macrophage-like cells labelled with radioactive cholesterol. Advanced biochemical testing can quantitate the pre-beta HDL particles considered most likely to effect reverse cholesterol transport. Nicholls and colleagues, in work with the laboratory of Rader (which has championed the in vitro assays of HDL function in cholesterol efflux from cells), have just published a very important and methodologically sound study in this regard. These investigators measured concentrations of pre-beta HDL and cholesterol efflux function in blood specimens derived from patients treated with evacetrapib. They documented substantial increases in pre-beta 1-HDL of >30% with doses of evacetrapib used in the recently halted clinical endpoint trial. They further found that evacetrapib treatment increased cholesterol efflux capacity from macrophage-like cells by about a third to a half, depending on the particular assay conditions. Thus, not only did this CETP inhibitor augment the very species of HDL thought to participate most prominently in reverse cholesterol transport, but also actually augmented cholesterol efflux capacity in vitro.

In the current context, these new data contribute to the confusion regarding HDL raising as a therapeutic strategy in preventing atherosclerotic events. Going well beyond mere HDL-C measurements by assaying quantitative and qualitative aspects of HDL widely believed to provide clinical benefit, the results of this new study would enhance the expectation that patients treated with evacetrapib should show reduced cardiovascular events. While we await details regarding the recently terminated clinical trial, from what we know today, there appears to be a shrinking dissociation between in vitro assessment of HDL properties considered important in mechanisms of benefit of HDL raising and clinical outcomes.

The particular aspects of HDL structure and function reported in this important paper by no means exhaust the possibility that other species of HDL for the manipulation of the functional properties of HDL or its prominent component apolipoprotein A1 (ApoA1) might yet yield clinical benefit. The abundance of the data regarding potential benefits that accrue from high HDL render further research in this field compelling, particularly in an era in which low-density lipoprotein cholesterol (LDL-C) control has advanced spectacularly. Yet, the current disappointment and the failure of functional tests of cholesterol efflux capacity to correlate with clinical benefit provide another sobering reminder that biomarkers of risk do not always constitute causal risk factors.

While recent genetic and functional data cast doubt on the protective effects of HDL-C elevation, in contrast, accumulating epidemiologic, mechanistic, and genetic data do support the atherogenicity of triglyceride-rich lipoproteins and the associated apolipoprotein C3. HDL and triglyceride concentrations tend to vary inversely; that is, high triglyceride concentrations often accompany low HDL and vice versa. For decades, investigators have found that adjusting triglyceride concentrations for HDL attenuates their correlation with cardiovascular risk. Such analyses have caused many to discard triglycerides as a causal risk factor. As I proposed in recent commentary ("Triglycerides on the Rise: Should We Swap Seats on the Seesaw"), perhaps we have confused the dependent and independent variable in such analyses, and lost our way by adjusting triglycerides for HDL, rather than the other way around.

We can draw several important conclusions from this state of affairs. First, no matter how compelling, observational data and biological plausibility do not necessarily predict the ability of a therapeutic manipulation of a biomarker to alter clinical outcomes. Second, we cannot forsake the arduous undertaking of large-scale clinical endpoint trials to evaluate novel therapeutics. The properly powered clinical trial provides the "acid test" for our conjectures, suppositions, and pet hypotheses. Practice trumps theory, and pursuit of "hard" clinical endpoints should and must remain the bedrock of informing our interventions to manage patients' cardiovascular risk. ■

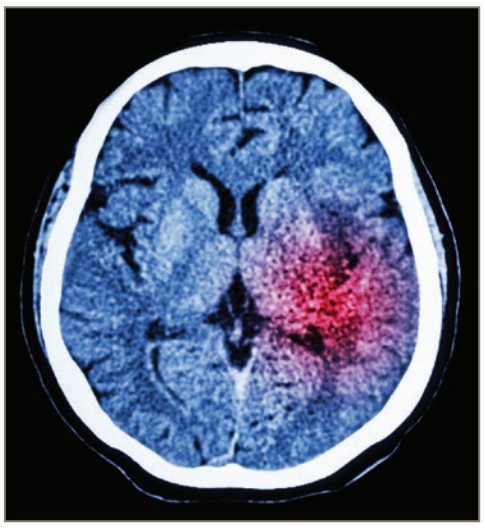
Peter Libby MD is Chief of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts; Mallinckrodt Professor of Medicine, Harvard Medical School, Boston, Massachusetts.

EXPERT OPINION

What is a reasonable time lapse after a prior stroke for alteplase?

BY DR JAMES C. GROTTA

Many of the so-called "exclusions" for stroke treatment with tPA are over 2 decades old and are derived directly from the inclusion/exclusion criteria of the original NINDS tPA stroke studies. These criteria were based on logic but few data and chosen very conservatively, primarily to minimise the risk of post-tPA bleeding. One that persists in both American and European guidelines is the 3-month rule for prior stroke as examined in a paper by Michal Karlinski and colleagues, published at the end of last year in *Stroke*.



Post-marketing databases give us the opportunity to examine how tPA is used in reality. The SITS registry is one of the best of these databases and was used by Dr Karlinski and his group to explore the risk of treating patients who had had a prior symptomatic cerebral infarct within 3 months of a later stroke. Incidence of symptomatic haemorrhage, death, and clinical outcome after tPA was no different in the 249 patients (2% of all tPA-treated patients in the registry) with prior stroke compared with patients who had no prior stroke, after adjustment for baseline differences in stroke severity, age, and other comorbidities.

There is a general sense among many clinicians that tPA should be withheld from "fragile" patients – that is, the elderly, previously disabled, and those with severe strokes. However, data from virtually all studies, including the Karlinski study, would argue the opposite. Because these patients will have such poor outcomes without treatment, tPA offers them the only option to regain an independent life. In the Karlinski study, 28% of patients with prior stroke were disabled and had more comorbidities, yet almost half ended up with a good outcome (mRS <2). Of course, clinical judgment should always prevail; the patients treated in the study were not randomised and undoubtedly were selected by clinicians as being "good" tPA candidates despite their prior stroke. Furthermore, this study provides no information on how soon after prior stroke tPA can be given. Presumably, most patients were treated toward the end of the 3-month interval. Biologically, the risk of bleeding from tPA should be related to disruption of the blood-brain barrier. This could probably last weeks after a stroke and might be more accurately gauged by looking for swelling or contrast enhancement on brain imaging than by simply counting the number of days elapsed. In my opinion, a 3-week rather than 3-month threshold is more reasonable. ■

New drugs and devices listing

THERAPEUTIC GOODS ADMINISTRATION www.tga.gov.au

Avanafil (Spedra), A Menarini – Erectile dysfunction
Cobimetinib (Cotellic), Roche – Unresectable or metastatic melanoma
Idarucizumab (rch) (Praxbind), Boehringer Ingelheim Reversal agent for dabigatran
Evolocumab (rch) (Repatha), Amgen Primary hypercholesterolaemia and homozygous familial hypercholesterolaemia
Follitropin alfa (rch) (Afolia/Bemfola), Finox Biotech Australia For the treatment of infertility.
Eltrombopag (Revolade), Novartis – Severe aplastic anaemia (SAA)
Ibrutinib (Imbruvica), Janssen-Cilag Small lymphocytic lymphoma (SLL), mantle cell lymphoma
Liraglutide (Saxenda), Novo Nordisk – For chronic weight management.
Enzalutamide (Xtandi), Astellas Pharma Metastatic castration-resistant prostate cancer

PHARMACEUTICAL BENEFITS SCHEME www.pbs.gov.au

Buprenorphine (Norspan), Mundipharma
Oxycodone + naloxone (Targin), Mundipharma
Paritaprevir + Ritonavir + Ombitasvir & Dasabuvir & Ribavirin (Viekira Pak-RBV), AbbVie
Sumatriptan (Imigran FDT), Aspen
Ustekinumab (Stelara), Janssen-Cilag
Nadroparin (Fraxiparine), Aspen
Rituximab (Mabthera SC), Roche
Sumatriptan (Imigran FDT), Aspen
Trastuzumab (Herceptin SC), Roche

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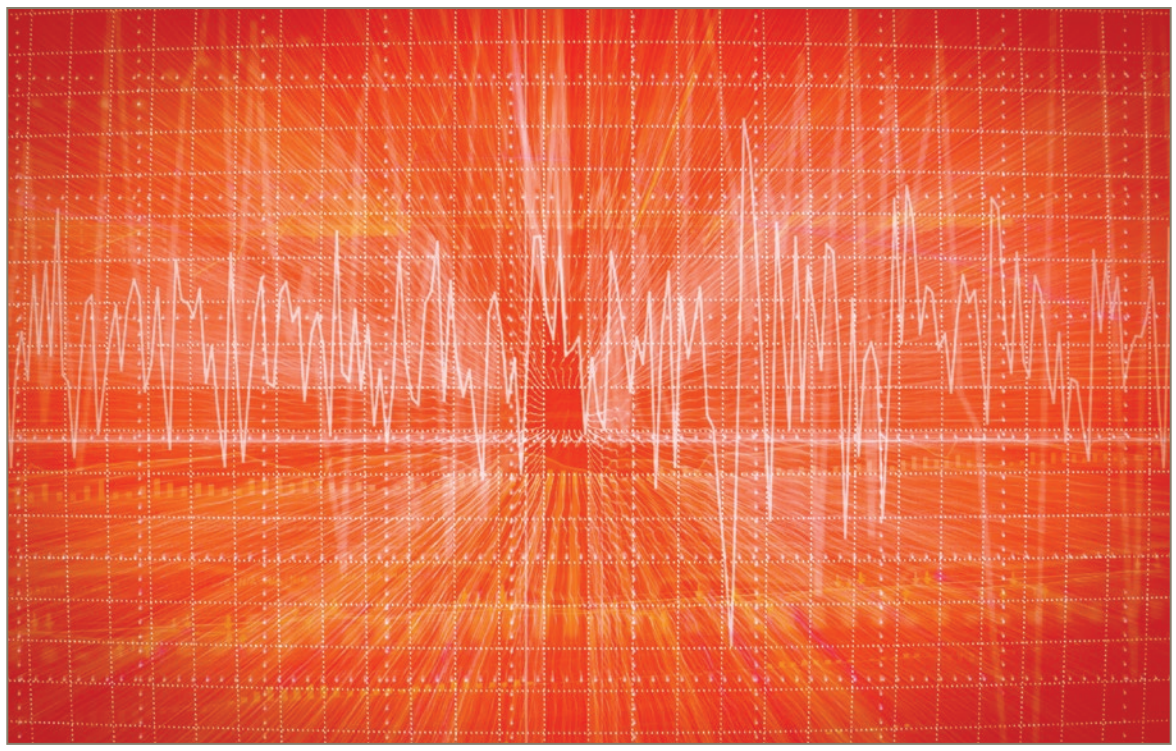
MY APPROACH

The evaluation of restrictive cardiomyopathy

BY DR CRAIG R ASHER AND DR ALLAN L KLEIN



Restrictive cardiomyopathy (RCM) was defined as a myocardial disease of unknown origin based on the WHO classification of 1980. Newer groupings of cardiomyopathy (CM) include the AHA classification, which distinguishes primary cardiac from systemic conditions, and the MOGE(S) system, which provides a detailed patient-specific description of (M) morphofunctional, (O) organ involvement, (G) genetic inheritance, (E) etiologic cause, and (S) stage of heart failure.

Nonetheless, the term RCM is still common vocabulary used to represent a heterogeneous group of disorders that arise from endomyocardial or myocardial disease resulting in a predominant disorder of advanced diastolic dysfunction. The differential diagnosis of these disorders includes isolated cardiac diseases and multisystem infiltrative or storage disorders. The prototype of RCM is cardiac amyloidosis (CA).

An important distinction to make prior to pursuing the work-up of RCM is to recognise that this term is not synonymous with restrictive physiology (RP) or a restrictive filling pattern. That is, RP can occur in conditions other than RCM, and RCM can occur without RP. RP refers to the presence of a high-left or right-sided filling pressure and poor chamber compliance. RP can occur with numerous conditions, some of which include atrial fibrillation, constrictive pericarditis, stiff left atrium syndrome, and coronary artery disease. It is important to distinguish RCM from constrictive pericarditis since the latter may be treated surgically.

RCM is usually suspected based on clinical presentation of heart failure, increased left ventricular wall thickness (WT), and abnormal diastolic function. CA is the most commonly encountered RCM, so testing should be targeted toward determining its presence. Other rare forms of RCM can be sought if CA is excluded. Since echocardiography is an initial diagnostic tool for heart failure patients, a differential diagnosis of pathologically increased WT should be considered and most often includes myocyte hypertrophy (hypertension, hypertrophic cardiomyopathy), myocardial storage (Fabry's, haemochromatosis), or inflammatory (sarcoidosis) or infiltrative disorders (CA). Concurrent with the echocardiographic interpretation of increased left ventricular WT, the electrocardiogram should be viewed for low voltage or voltage-mass mismatch, a feature that is consistent but not specific for CA.

Classical features of CA by echocardiography include biventricular increased WT without cavity dilation, a "granular sparkling" appearance, biatrial enlargement, thickened valves and atrial septum, pericardial effusion, pulmonary hypertension, and advanced, often grade 3, diastolic dysfunction with an elevated mitral E/A ratio (>2), short deceleration time (<150 ms), very low tissue Doppler annular velocities (<6 cm/s), and an elevated mitral E/e' ratio (>15). Systolic anterior motion of the mitral valve may uncommonly occur with CA. All patients with suspected CA should have analysis of longitudinal strain looking for the characteristic apical-sparing pattern, which is not typical of most other RCMs.

With a suspected diagnosis of CA based on clinical history, electrocardiography, and echocardiography with an apical-sparing pattern, confirmatory testing should be performed. Laboratory testing includes: serum and urine protein electrophoresis and immunofixation; serum-free light chains (K:L ratio); and transthyretin (TTR), often with complementary bone marrow biopsy. Cardiac MRI and 99mTc are increasingly useful to assess alternative diagnoses and discriminate between AL (primary amyloidosis) and TTR CA. Tissue or cardiac biopsy can be done selectively when the diagnosis remains equivocal or as mandated for trial inclusion.

RCM should not be considered a futile diagnosis. Specific diagnosis is crucial, especially among amyloid subtypes (AL; TTR wild-type and mutant). Heart failure management differs from conventional treatment. Advocacy groups including the Amyloid Foundation, genetic counselling (for familial amyloid), clinical trials, and local and national referral centers to haematology and cardiology experts are encouraged.

Craig R Asher MD is cardiologist at Cleveland Clinic Florida, Weston.

Allan L Klein MD is director of the Centre for the Diagnosis and Treatment of Pericardial Diseases and a staff cardiologist in the Section of Cardiovascular Imaging, Department of Cardiovascular Medicine, Heart & Vascular Institute of Cleveland Clinic, Cleveland.

JOURNAL SCAN

LGE provides incremental prognostic information over serum biomarkers in AL cardiac amyloidosis

JACC: Cardiovascular Imaging

Take-home message

- A retrospective analysis was conducted of the prognostic value of cardiac magnetic resonance (CMR) late gadolinium enhancement (LGE) in the diagnosis of amyloid light-chain (AL) amyloidosis. In total, 76 patients with AL amyloidosis confirmed by histology underwent CMR LGE imaging. LGE was reported as global, focal patchy, or none. Over the course of 34.4 months, 40 patients died and global LGE correlated positively with all-cause mortality (HR, 2.93; P < 0.001). In multivariate analysis with biomarker staging, global LGE still showed a significant association with increased mortality (HR, 2.43; P = 0.01).
- Global LGE on CMR is a helpful prognostic indicator in patients with AL cardiac amyloidosis.

OBJECTIVES This study sought to determine the prognostic value of cardiac magnetic resonance (CMR) late gadolinium enhancement (LGE) in amyloid light chain (AL) cardiac amyloidosis.

BACKGROUND Cardiac involvement is the major determinant of mortality in AL amyloidosis. CMR LGE is a marker of amyloid infiltration of the myocardium. The purpose of this study was to evaluate retrospectively the prognostic value of CMR LGE for determining all-cause mortality in AL amyloidosis and to compare the prognostic power with the biomarker stage.

METHODS Seventy-six patients with histologically proven AL amyloidosis underwent CMR LGE imaging. LGE was categorised as global, focal patchy, or none. Global LGE was considered present if it was visualised on LGE images or if the myocardium nulled before the blood pool on a cine multiple inversion time (TI) sequence. CMR morphologic and functional evaluation, echocardiographic diastolic evaluation, and cardiac biomarker staging were also performed. Subjects' charts were reviewed for all-cause mortality. Cox proportional hazards analysis was used to evaluate survival in univariate and multivariate analysis.

RESULTS There were 40 deaths, and the median study follow-up period was 34.4 months. Global LGE was associated with all-cause mortality in univariate analysis (hazard ratio = 2.93; P < 0.001). In multivariate modeling with biomarker stage, global LGE remained prognostic (hazard ratio = 2.43; P = 0.01).

CONCLUSIONS Diffuse LGE provides incremental prognosis over cardiac biomarker stage in patients with AL cardiac amyloidosis.

LGE Provides Incremental Prognostic Information Over Serum Biomarkers in AL Cardiac Amyloidosis *JACC Cardiovasc Imaging* 2016 May 11; [EPub Ahead of Print], SJ Boynton, JB Geske, A Dispenzieri, et al

JOURNAL SCAN

Right ventricular function in peripartum cardiomyopathy is associated with left ventricular recovery

Circulation: Heart Failure

Take-home message

- The authors evaluated 100 peripartum cardiomyopathy patients (LVEF <45% within 13 weeks) to determine if RV function was associated with LV recovery (LVEF ≥50% at 1 year) and clinical outcomes. LV recovery was attained in 75%, and 13% had LVEF of ≤35% or major adverse events. Right ventricular fractional area change was independently associated with LV recovery.
- In this cohort of pregnancy-related cardiomyopathy patients, right ventricular function assessed through right ventricular fractional area change was independently associated with LV recovery.

BACKGROUND Peripartum cardiomyopathy has variable disease progression and left ventricular (LV) recovery. We hypothesised that baseline right ventricular (RV) size and function are associated with LV recovery and outcome.

METHODS AND RESULTS Investigations of Pregnancy-Associated Cardiomyopathy was a prospective 30-centre study of 100 peripartum cardiomyopathy women with LV ejection fraction (LVEF) <45% within 13 weeks after delivery. Baseline RV function was assessed by echocardiographic end-diastolic area, end-systolic area, fractional area change, tricuspid annular plane excursion, and RV speckle-tracking longitudinal strain. LV recovery was defined as LVEF of ≥50% at 1 year, persistent severe LV dysfunction as LVEF of ≤35%, and major events as death, transplant, or LV assist device implantation. RV measurements were feasible for 90 of the 96 patients (94%) with echocardiograms available. Mean baseline LVEF was 36 ± 9%. RV fractional area change was <35% in 38% of patients. Of 84 patients with 1-year follow-up data, 63 (75%) had LV recovery and 11 (13%) had LVEF of ≤35% or a major event (4 LV assist devices and 2 deaths). Tricuspid annular plane excursion and RV strain did not predict outcome. Baseline RV fractional area change by multivariable analysis was independently associated with subsequent LV recovery and clinical outcome.

CONCLUSIONS Peripartum cardiomyopathy patients had a high incidence of LV recovery, but a significant minority had persistent LV dysfunction or a major clinical event by 1 year. RV function per echocardiographic fractional area change at presentation was associated with subsequent LV recovery and clinical outcomes and thus is prognostically important.

Right Ventricular Function in Peripartum Cardiomyopathy at Presentation Is Associated With Subsequent Left Ventricular Recovery and Clinical Outcomes *Circ Heart Fail* 2016 May 01;9(5)e002756, LA Blauwet, A Delgado-Montero, K Ryo, et al.

EXPERT OPINION

Tapping the potential of T1 mapping

BY DR MARTIN S MARON

Differentiating left ventricular (LV) wall thickening due to a genetically determined cardiomyopathic process, such as hypertrophic cardiomyopathy (HCM), from hypertrophy secondary to pressure overload (such as in systemic hypertension), has historically represented a clinical challenge in general cardiology practice. This diagnostic dilemma often has important implications for management. This is particularly the case in patients with systemic hypertension and a maximal LV wall thickness of up to 18 mm and without evidence of subaortic obstruction, since hypertensive cardiomyopathy is very rarely associated with outflow obstruction due to typical mitral valve-septal contact. In this regard, numerous advances in cardiovascular magnetic resonance (CMR) provide the opportunity to characterise the abnormal myocardial tissue in order to differentiate diseases with overlapping phenotypes of increased LV wall thickness.

With the technique of contrast-enhanced CMR, intravenous gadolinium is deposited in the myocardium, resulting in unique late gadolinium enhancement (LGE) patterns specific to certain disease states. For example, the distribution and pattern of LGE in cardiac amyloid is different from that in HCM, providing the potential to reliably differentiate between these two diseases. More recently, T1 mapping has emerged as an additional CMR-based technique, which may overcome some of the technical limitations associated with LGE imaging. With native T1 mapping, the myocardial tissue is probed to assess diffuse interstitial expansion, while LGE is mainly detecting focal areas of fibrosis.

In the 2015 study conducted by Hinojar and colleagues, native T1 values were significantly greater in HCM patients compared with patients with hypertensive cardiomyopathy, including hypertensive patients with more significant hypertrophy (wall thickness >15 mm).[1] In multivariate regression analysis, native T1 was identified as a strong independent parameter in differentiating HCM from hypertensive cardiomyopathy, associated with high discriminatory accuracy. T1 values were also greater in a small cohort of genotype positive/phenotype negative HCM family members compared with controls, suggesting that early changes to the underlying myocardial substrate may be detected using T1 mapping even in the absence of a clinical diagnosis of LV hypertrophy.

These results from the Hinojar study provide further opportunity for optimism that novel CMR-based techniques, such as native T1 mapping (and LGE), represent powerful imaging biomarkers capable of characterising the interstitial compartment to improve diagnostic capabilities. However, important limitations to measuring T1 will need to be addressed before it can ultimately be reliably integrated into clinical practice, including standardising the approach to T1 measurements to achieve reproducible measurements among centres (and different vendors), as well as with varying magnet strengths. Nevertheless, numerous potential applications are now emerging in which T1 mapping may become an important clinical tool, including greater accuracy in noninvasive differentiation among other overlapping cardiac phenotypes of increased LV wall thickness, such as differentiating HCM from athlete's heart, Fabry disease, and amyloid cardiomyopathy.

In addition, T1 mapping may also provide the opportunity to more precisely characterise the HCM phenotype to detect HCM family members who may have evidence of alterations in myocardial structure that precede the development of LV hypertrophy and therefore permit early recognition and closer follow-up for detection of clinical disease. Furthermore, T1 mapping, representing a sensitive marker of the underlying adverse substrate of HCM, could be used to assess the impact of emerging novel therapies targeted at improving the HCM phenotype.

This is an exciting period for imaging in cardiovascular disease, and T1 mapping continues to generate much enthusiasm as a developing technique with the potential for having substantial clinical impact on diagnosis and management strategies.

1. Hinojar R, Varma N, Child N, et al. T1 mapping in discrimination of hypertrophic phenotypes: hypertensive heart disease and hypertrophic cardiomyopathy: findings from the International T1 Multicenter Cardiovascular Magnetic Resonance Study. *Circ Cardiovasc Imaging.* 2015 Dec;8(12): e003285.

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JOURNAL SCAN

Scar detection by pulse-cancellation echocardiography: validation by CMR in patients with recent STEMI

JACC: Cardiovascular Imaging

Take-home message

- The authors evaluated scar imaging echocardiography with ultrasound multi-pulse scheme (eSCAR) in 35 patients (20 with STEMI and 15 negative controls) compared with cardiac magnetic resonance assessing late gadolinium enhancement (CMR-LGE). Results showed scar detection by echocardiography was 100% compared with 91% by CMR-LGE, although there was under-sensitivity in the most apical segments with eSCAR.
- Multi-pulse echocardiography matched CMR-LGE in presence and site of scar detection in patients 30 days after STEMI, and there were no false positives in the control group.

Dr James E Udelson

Detection of the presence and extent of myocardial infarction has clear clinical importance. In this study, the authors adapt an echocardiographic technique using a pulse cancellation ultrasound wave reflection method, which they refer to as scar imaging echocardiography, or eSCAR. They use eSCAR to assess the presence, location, and extent of MI in a very small group of recent STEMI patients and controls, using late gadolinium–enhanced cardiac MR (LGE CMR) as the gold standard. While they report good performance for assessing the presence or absence of infarct with eSCAR compared with LGE CMR, as well as general localization, the eSCAR technique clearly underestimates the extent of infarct, particularly so in the important LAD territory infarcts. The apical segments were also very suboptimally assessed by eSCAR. Analysis of the technique requires the ability to differentiate the bright scar from other echo-enhanced structures such as the pericardium and chordae among others, and a variant referred to as "septal stripes," which the authors acknowledge requires a learning curve. At this early stage of development, only the most basic "yes/no any infarct" question seems to be answered, and whether any further refinements may enable better correlation with the true extent of infarct, or whether performance may be maintained in the more challenging non-transmural infarct/NSTEMI population, remains to be seen.

Abstract

OBJECTIVES This study sought to assess an echocardiographic approach (scar imaging echocardiography with ultrasound multipulse scheme [eSCAR]), based on existing multipulse ultrasound scheme, as a marker of myocardial scar in humans, compared with cardiac magnetic resonance assessing late gadolinium enhancement (CMR-LGE).

BACKGROUND The detection of myocardial scar impacts patient prognosis and management in coronary artery disease and other types of cardiac disease. The clinical experience with echocardiography suggests that the reflected ultrasound signal is often significantly enhanced in infarcted myocardial segments.

METHODS Twenty patients with a recent ST-segment elevation myocardial infarction (STEMI) (cases) and fifteen patients with absent CMR-LGE (negative controls) were imaged with both the eSCAR pulse-cancellation echo and CMR-LGE to assess their potential association.

RESULTS Scar was detectable at CMR-LGE in 19 of 20 STEMI patients (91%), whereas all (100%) demonstrated eSCAR at echocardiography. In the 19 STEMI patients in whom CMR-LGE was detected, regional matching between eSCAR and CMR-LGE was total, although the segmental extent of detected scar was not always superimposable, particularly in the most apical segments, a region in which eSCAR demonstrated undersensitivity for the true extent of scar.

CONCLUSIONS A 2-dimensional multipulse echocardiography allows detection of myocardial scar, reliably matching the presence and site of CMR-LGE at 30 days after STEMI, or its absence in negative controls.

Scar detection by pulse-cancellation echocardiography: validation by CMR in patients with recent STEMI *JACC Cardiovasc Imaging* 2016 May 13; [EPub Ahead of Print], N Gaibazzi, M Bianconcini, N Marzziliano, et al.

JOURNAL SCAN

Rare mutation in ASGR1 is associated with a reduced risk of CAD

The New England Journal of Medicine

Take-home message

- The authors evaluated the association between genetic variants and levels of non-HDL cholesterol. The risk of CAD in 42,524 case patients and 249,414 controls from European populations was assessed. Results showed that a heterozygous carrier of the del12 mutation of ASGR1 confirmed a 15.3 mg/dl-lower level of non-HDL cholesterol, producing a 34% lower risk of CAD ($P = 4.0 \times 10^{-6}$). Another ASGR1 variant, p.W158X, also conferred a lower level of non-HDL cholesterol.
- The rare del12 mutation of ASGR1 was associated with lower levels of non-HDL cholesterol and a lower risk of CAD.

Dr Heribert Schunkert

Less is more when it comes to the activity of the asialoglycoprotein receptor (ASGR1). In the paper by Nioi and colleagues from Iceland, a large-scale genomic strategy was applied to identify a rare variant that is related to lower non-HDL cholesterol levels, lower incidence of coronary artery disease, and a somewhat prolonged life expectancy. The paper is remarkable for two reasons. First, the authors sequenced genomes of more than 2600 Icelanders and found millions of genetic variants that allowed them to impute on a high-resolution scale these variants into almost 400,000 Icelanders. Using this extraordinary large sample, the authors successfully identified a rare noncoding 12-base pair deletion in intron 4 of ASGR1. This lectin plays a role in the homeostasis of circulating glycoproteins. The deletion activates a cryptic splice site that leads to frameshift mutation and a shorter protein that is prone to rapid degradation.

In the study population, 1 in 120 persons carried the mutation and was characterised by, on average, 15 mg/dL lower non-HDL cholesterol as well as a 34% reduction in coronary artery disease risk. Second, a new mechanism is described that affects lipid metabolism. In addition to lower LDL, the authors observed a small increase in HDL cholesterol and a small decrease in triglyceride levels related to this variant. Moreover, alkaline phosphatase as well as vitamin B12 levels were remarkably higher in those individuals who carried the genetic variant.

The paper also offers a rationale for therapeutic intervention in that neutralisation of ASGR1 may beneficially affect lipid metabolism. Moreover, such intervention appears to be safe, since no risks were observed in those who carried the mutation. From this perspective, it is interesting that the Icelandic company DeCODE was taken over by Amgen, which appears to work on strategies to translate this genetic finding into clinical applications.

Abstract

BACKGROUND Several sequence variants are known to have effects on serum levels of non-high-density lipoprotein (HDL) cholesterol that alter the risk of coronary artery disease.

METHODS We sequenced the genomes of 2636 Icelanders and found variants that we then imputed into the genomes of approximately 398,000 Icelanders. We tested for association between these imputed variants and non-HDL cholesterol levels in 119,146 samples. We then performed replication testing in two populations of European descent. We assessed the effects of an implicated loss-of-function variant on the risk of coronary artery disease in 42,524 case patients and 249,414 controls from five European ancestry populations. An augmented set of genomes was screened for additional loss-of-function variants in a target gene. We evaluated the effect of an implicated variant on protein stability.

RESULTS We found a rare noncoding 12-base-pair (bp) deletion (del12) in intron 4 of ASGR1, which encodes a subunit of the asialoglycoprotein receptor, a lectin that plays a role in the homeostasis of circulating glycoproteins. The del12 mutation activates a cryptic splice site, leading to a frameshift mutation and a premature stop codon that renders a truncated protein prone to degradation. Heterozygous carriers of the mutation (1 in 120 persons in our study population) had a lower level of non-HDL cholesterol than noncarriers, a difference of 15.3 mg per deciliter (0.40 mmol per liter) (P=1.0×10(-16)), and a lower risk of coronary artery disease (by 34%; 95% confidence interval, 21 to 45; P=4.0×10(-6)). In a larger set of sequenced samples from Icelanders, we found another loss-of-function ASGR1 variant (p.W158X, carried by 1 in 1850 persons) that was also associated with lower levels of non-HDL cholesterol (P=1.8×10(-3)).

CONCLUSIONS ASGR1 haploinsufficiency was associated with reduced levels of non-HDL cholesterol and a reduced risk of coronary artery disease. (Funded by the National Institutes of Health and others.).

Variant ASGR1 Associated With a Reduced Risk of Coronary Artery Disease *N Engl J Med* 2016;374(22)2131–2141, P Nioi, A Sigurdsson, G Thorleifsson,et al.

EXPERT OPINION

Vagal nerve stimulation for heart failure

BY DR SAMUEL J ASIRVATHAM, DR CHANCE M WITT AND DR SURAJ KAPA

Modulation of the autonomic nervous system may be the next leap forward in treatment of heart failure, a disease characterised by high sympathetic tone. One method of autonomic modulation is through stimulation of the vagus nerve with an implanted electrical device, a treatment used successfully in refractory epilepsy for years. While abundant preclinical data suggest the efficacy of this type of treatment in heart failure, substantial clinical trials have only recently begun to take place.[1,2] The results of these trials have been heterogeneous and not entirely positive. This may stem from a lack of knowledge regarding the precise expected benefits and the appropriate "dose" of therapy.

Autonomic modulation has already been shown to be effective in other realms of cardiology, particularly for the treatment of arrhythmias.[3,4] Atrial fibrillation may be more effectively treated with the concomitant ablation of autonomic ganglia surrounding the heart, potentially reducing their negative effects on the underlying myocardium.[5,6] Studies have also shown that cardiac sympathetic denervation may be an effective preventative and curative treatment in certain types of ventricular arrhythmia.[7,8] This treatment theoretically works by removing sympathetic input to the heart. While vagal nerve stimulation (VNS) may be most simply thought to increase the parasympathetic tone to the heart, it also appears to decrease sympathetic input through afferent signalling and other feedback mechanisms, providing another potential mechanism of benefit.[9]

A study by Libbus and colleagues published in *Heart Rhythm* provides further insight into these areas of limited knowledge by assessing variables associated with autonomic function and ventricular arrhythmia in a subset of 25 patients from the ANTHEM-HF trial who underwent 24-hour ECG monitoring.[10] Overall, they show that autonomic regulation therapy in the form of VNS seems to have a normalising effect on markers of autonomic function and arrhythmia susceptibility at 6 and 12 months after initiation.

Autonomic function was assessed by evaluation of several permutations of heart rate variability and heart rate turbulence. The latter pertains to the change in heart rate after a premature ventricular contraction and is modulated by the autonomic nervous system. It has also been shown to be associated with mortality and sudden death in heart failure.[11] The study by Libbus and colleagues showed a significant improvement in this measure as well as expected changes in heart rate variability associated with increased vagal tone.

Variation in T-wave morphology, known as T-wave alternans, has been shown to be a predictor of sudden cardiac death.[12] Libbus and colleagues found that VNS was associated with a significant reduction in this T-wave variability and the reduction was noted to be greater with high- vs low-intensity stimulation. Furthermore, the number of patients having nonsustained episodes of ventricular tachycardia decreased from 11 of 25 prior to therapy to 3 of 25 at the end of 12 months.

The study by Libbus et al demonstrates that VNS does appear to increase parasympathetic tone and baroreflex sensitivity as reflected in the measurements of heart rate variability and turbulence. More importantly, this treatment potentially reduces ventricular arrhythmogenicity as shown by normalisation of T-wave alternans. The presumed objective of VNS in heart failure patients has been to reduce symptoms and mortality through reverse remodelling and increasing ejection fraction. However, these findings suggest that we should also consider the prevention of sudden cardiac death as an objective, more similar to the expectations associated with an implantable cardioverter-defibrillator. These results also support the possibility of using VNS for ventricular arrhythmia without heart failure. Lastly, the apparent dose-response seen here reminds us to continue to consider all of the variables that are involved with VNS with regard to pulse width, frequency, amplitude, side, et cetera. This is not an all-or-none treatment.

All of the findings in the Libbus study are only surrogate endpoints, and we will eventually need to see improvements in hard endpoints before extensive adoption of VNS as a therapeutic option. However, studies like this are necessary to provide the framework for designing those larger trials. ■

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NEWS

Few people with very high cholesterol harbour key mutations, but those who do face a high CAD risk

Very high cholesterol can be attributed to a genetic mutation related to familial hypercholesterolaemia in only a small fraction of people. Such individuals, however, face a high risk of developing early-onset coronary artery disease (CAD). These findings were reported at the American College of Cardiology's 65th Annual Scientific Session.

Amit V. Khera, MD, and Sekar Kathiresan, MD, both of Massachusetts General Hospital, Boston, performed the largest gene sequencing analysis to date focusing on individuals with very high cholesterol.

Their first objective was to determine the prevalence of a familial hypercholesterolaemia mutation among people with low-density lipoprotein (LDL) cholesterol levels ≥6.78 µmol/L

Studies have suggested a mutation prevalence >25%, but these studies have been limited to people with additional risk factors, such as a family history of high cholesterol, an abnormal physical exam, or the development of high cholesterol at an early age, in addition to LDL cholesterol ≥6.78 µmol/L. The present study was the largest to assess for familial hypercholesterolaemia mutations among a broad population of people with elevated cholesterol.

The study's second objective was to examine the health impacts of a familial hypercholesterolaemia mutation beyond elevated cholesterol. Drs. Khera and Kathiresan focused on early-onset CAD (in men before 55 or women before age 65 years).

Dr Khera said, "Many clinicians assume that patients with LDL ≥6.78 µmol/L have a familial hypercholesterolaemia mutation as the major driver. But many causes can underlie this very high LDL, such as poor diet, lack of exercise, and a variety of common genetic variants that each exert a small impact on cholesterol but together can add up to a large impact."

Drawing on genetic information from several large research studies, representing a total of more than 26,000 people, the team identified individuals with mutations in any of three known familial hypercholesterolaemia genes.

People with LDL cholesterol ≥6.78 µmol/L but no familial hypercholesterolaemia mutation were at six times higher risk of early-onset CAD than those with LDL <4.64 µmol/L (considered average). Of people with LDL cholesterol ≥6.78 µmol/L, only 2% harboured a familial hypercholesterolaemia mutation. Yet these individuals faced a 22 times higher risk of early-onset CAD.

Though the increased risk was especially pronounced in those with LDL cholesterol ≥6.78 µmol/L, people with a familial hypercholesterolaemia mutation faced a substantially increased CAD risk even when their cholesterol level was only mildly elevated.

Dr Khera said, "One of the reasons for this increased risk is that if you have a mutation, your cholesterol is elevated from the time of birth. We think the cumulative exposure to LDL cholesterol over the course of a lifetime is the important factor."

Drs. Khera and Kathiresan extrapolated the result to estimate that 412,000 of about 14 million adult Americans with an untreated LDL ≥6.78 µmol/L harbour a familial hypercholesterolaemia mutation.

The findings raise the question of whether to screen for the mutations in all individuals with high LDL cholesterol. While such screening could potentially help doctors and patients proactively try to reduce CAD risk, a host of psychological and ethical issues need to be considered before widespread implementation.

Dr Khera concluded, "If you performed widespread genetic screening of all individuals with very high LDL cholesterol, your yield would likely be low, but for people with the mutations, the results could be quite meaningful."

Limitations of the study were that it focused on patients with early-onset CAD, rather than all CAD patients, and that it defined familial hypercholesterolaemia as a mutation in one of three genes for the disease: LDL receptor, apolipoprotein B, and proprotein convertase subtilisin/kexin type 9. Ongoing work may identify additional genes.

Lastly, Drs. Khera and Kathiresan did not have access to a detailed physical exam or family histories to enable direct comparisons. Nevertheless the study was adequately powered to address its primary endpoint. ■

JOURNAL SCAN

Clinical and functional outcomes of atrial fibrillation in women and men

JAMA Cardiology

Take-home message

- A cohort of 10,135 patients with atrial fibrillation (AF) was analysed to evaluate the differences in symptoms, quality of life, treatment, and outcomes in men and women.
- Women with AF were older with higher CHA2DS2-VASc scores than their male counterparts, but they experienced less sleep apnoea. Women experienced a worse quality of life than men, with 32.1% of women reporting no symptoms due to AF vs 42.5% of men. Rates of anticoagulation and time in therapeutic range were similar in the two groups. Women had lower all-cause mortality and cardiovascular death rates but a higher risk for stroke or embolism than men.

IMPORTANCE Despite the frequency of atrial fibrillation (AF) in clinical practice, relatively little is known about sex differences in symptoms and quality of life and how they may affect treatment and outcomes.

OBJECTIVES To determine whether symptoms, quality of life, treatment, and outcomes differ between women and men with AF.

DESIGN, SETTING, AND PARTICIPANTS This observational cohort study included 10 135 patients with AF. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation is a prospective, nationwide, multicentre outpatient registry of patients with incident and prevalent AF enrolled at 176 sites between June 2010 and August 2011.

MAIN OUTCOMES AND MEASURES Symptoms, quality of life as measured by Atrial Fibrillation Effects on Quality of Life scores, AF treatment, cardiovascular outcomes, stroke or non-central nervous system embolism, and all-cause mortality.

RESULTS Overall, 4293 of the cohort (42%) were female. Compared with men, women were older (77 years; interquartile range [IQR], 69-83, vs 73 years; IQR, 65–80; P<0.001) and had higher median CHA2DS2-VASc scores (5; IQR, 4–6, vs 3; IQR, 2–5; P<0.001), but less sleep apnoea (578 [13.5%] vs 1264 [21.6%]; P<0.001). Only 32.1% of women (n=1378) were asymptomatic (European Heart Rhythm Association class I) compared with 42.5% of men (n=2483) in unadjusted analyses (P<0.001). Women had lower (more severe) unadjusted baseline overall Atrial Fibrillation Effects on Quality of Life scores (n=2007; 80; IQR, 62–92 vs 83; IQR, 69–94; P<0.001). Women had similar rates of anticoagulation and similar time in therapeutic range. In follow-up, women experienced lower risk-adjusted all-cause mortality (adjusted hazard ratio, 0.57; 95% CI, 0.49–0.67) and cardiovascular death (adjusted hazard ratio, 0.56; 95% CI, 0.44–0.72); however, they had a higher risk for stroke or non-central nervous system embolism (adjusted hazard ratio, 1.39; 95% CI, 1.05–1.84; P=0.02) compared with men.

CONCLUSIONS AND RELEVANCE Women with AF have more symptoms and worse quality of life. Despite higher risk, women have lower risk-adjusted all-cause and cardiovascular death compared with men, but higher stroke rates. Future studies should focus on how treatment and interventions specifically affect AF-related quality of life and cardiovascular outcomes in women.

Differences in clinical and functional outcomes of atrial fibrillation in women and men: two-year results from the ORBIT-AF registry. *JAMA Cardiol* 2016;[EPub ahead of print], JP Piccini, DN Simon, BA Steinberg, et al.

JOURNAL SCAN

Novel method for earlier detection of phrenic nerve injury during cryoballoon ablation

Heart Rhythm

Take-home message

- The authors examined a new method for the earlier prediction of phrenic nerve palsy (PNP) to improve recovery times in 197 patients undergoing cryoballoon ablation (CB-A) of bilateral pulmonary veins. Monitoring of the phrenic nerve was accomplished through fluoroscopic images of diaphragmatic contractions and compound motor action potentials (CMAP). Results showed that pacing with MIN output detected PNP earlier than MAX (P < 0.01), which resulted in shorter recovery (P < 0.001).
- Recovery from PNP improved from months to hours post-operatively by utilising an improved method of pacing with the minimum output.

BACKGROUND Diaphragmatic electrogram recording during cryoballoon ablation (CB-A) of atrial fibrillation is commonly utilised to predict phrenic nerve palsy (PNP).

OBJECTIVE We investigated a novel method for predicting PNP at an earlier stage to prevent sustained PNP.

METHODS A total of 197 patients undergoing CB-A were enrolled. We attempted to detect PNP using fluoroscopic images of diaphragmatic contractions and by monitoring diaphragmatic compound motor action potentials (CMAP) provoked by superior vena cava (SVC)/and left subclavian vein (LCV) pacing during CB-A for bilateral pulmonary veins (PVs). Pacing of the SVC and LCV was performed at two outputs, one exceeding the pacing threshold by 10% (MIN) and the other at maximum output (MAX). The time from freezing to the initiation of PNP, values of the CMAP amplitude, and severity of PNP were compared for the two outputs.

RESULTS There was a significant difference in the time from freezing to initiation of PNP between MIN and MAX pacing (25.7 ± 5.7 vs 81.3 ± 7.4 sec, P < 0.01). The CMAP amplitudes also differed significantly (0.71 ± 0.39 vs 1.13 ± 0.42, P < 0.0001). SVC/LCV pacing with MIN output was able to detect PNP significantly earlier than MAX (27 ±8 vs 91 ±12 sec, P < 0.01), and the time to PNP recovery was significantly shorter for the MIN output (20.2 ± 8.88 hours vs 4.8 ± 1.6 months, P < 0.001).

CONCLUSION Pacing the SVC and LCV with lower output detect PNP significantly earlier than maximal output pacing and leads to recovery from PNP on the order of hours post-procedure, rather than months.

Novel method for earlier detection of phrenic nerve injury during cryoballoon applications for electrical isolation of pulmonary veins in patients with atrial fibrillation. *Heart Rhythm* 2016; [EPub Ahead of Print], K Okishige, H Aoyagi, N Kawaguchi, et al.

JOURNAL SCAN

Effect of left atrial appendage excision on procedure outcome in patients with persistent atrial fibrillation undergoing surgical ablation

Heart Rhythm

Take-home message

- The authors randomly assigned 176 patients with persistent atrial fibrillation to two surgical groups to evaluate the efficacy of LAA excision with an 18-month follow-up. The two groups were pulmonary vein isolation (PVI) + box lesion vs PVI + box lesion + LAA excision. There were no significant differences in freedom from atrial fibrillation with or without antiarrhythmic medication and no significant differences in adverse events between the two groups.
- No improvement in atrial fibrillation or decrease in adverse events was found with adding LAA to PVI and box lesion surgical intervention for persistent atrial fibrillation.

BACKGROUND Catheter ablation is less successful for persistent atrial fibrillation (PersAF) than for paroxysmal atrial fibrillation. Some studies suggest that left atrial appendage (LAA) isolation in addition to pulmonary vein isolation (PVI) is required to maximise benefits for PersAF after ablation.

OBJECTIVE To compare the efficacy and safety of two surgical ablation approaches for PersAF via video-assisted thoracoscopic: PVI + box lesion and PVI + box lesion + LAA excision.

METHODS We randomly assigned 176 patients with PersAF to video-assisted thoracoscopic surgical ablation with PVI + box lesion (88 patients) or PVI + box lesion + LAA excision (88 patients). The primary endpoint was freedom from any documented atrial arrhythmia lasting longer than 30 seconds after a single ablation procedure without antiarrhythmic drug (AAD).

RESULTS After 18 months of follow-up, 61 (70.9%) out of 86 patients assigned to PVI + box lesion were free from recurrent AF, as compared with 64 (73.6%) out of 87 patients assigned to PVI + box lesion + LAA excision after a single ablation procedure without AAD (P = 0.73). Freedom from any atrial arrhythmia after single procedure with or without AAD was also nonsignificant: 70.9% vs 74.7%, respectively. There were no significant differences in adverse events between groups, including death, transient ischaemic attack, stroke, pneumothorax and hydrothorax.

CONCLUSIONS Among patients with persAF, we found no reduction in the rate of recurrent AF when LAA excision was performed in addition to PVI and box lesion during surgical ablation.

Effect of left atrial appendage excision on procedure outcome in patients with persistent atrial fibrillation undergoing surgical ablation *Heart Rhythm* 2016; [EPub Ahead of Print], A Romanov, E Pokushalov, D Elesin, et al.

JOURNAL SCAN

Current interventions effective for stroke prevention in atrial fibrillation

Journal of the American Heart Association

Take-home message

- The authors of this study performed a meta-analysis of 21 randomised clinical trials that included 96,017 patients with nonvalvular atrial fibrillation (AF). They evaluated efficacy of novel oral anticoagulants (NOACs; apixaban, dabigatran, edoxaban, and rivaroxaban), vitamin K antagonists, aspirin, and the Watchman device in reducing the combination of stroke and systemic embolism (primary outcome) and all-cause mortality (secondary outcome). They also evaluated these interventions for safety using combined rates of major extracranial bleeding and intracranial haemorrhage. All treatments were found to reduce risk of stroke and systemic embolism significantly and all-cause mortality in patients with nonvalvular AF compared with placebo. Apixaban, dabigatran, and edoxaban were also found to significantly reduce risk of all-cause death when compared with vitamin K antagonists.
- All currently accepted treatments for nonvalvular AF result in significant reduction in stroke/systemic embolism and all-cause mortality, although the efficacy differs between drug classes.

BACKGROUND The goal of this study was to compare the safety and effectiveness of individual antiembolic interventions in nonvalvular atrial fibrillation (AF): novel oral anticoagulants (NOACs) (apixaban, dabigatran, edoxaban, and rivaroxaban); vitamin K antagonists (VKA); aspirin; and the Watchman device.

METHODS AND RESULTS A network meta-analysis of randomised, clinical trials (RCTs) was performed. RCTs that included patients with prosthetic cardiac valves or mitral stenosis, mean or median follow-up <6 months, <200 participants, without published report in English language, and NOAC phase II studies were excluded. The placebo/control arm received either placebo or no treatment. The primary efficacy outcome was the combination of stroke (of any type) and systemic embolism. All-cause mortality served as a secondary efficacy outcome. The primary safety outcome was the combination of major extracranial bleeding and intracranial hemorrhage. A total of 21 RCTs (96 017 nonvalvular AF patients; median age, 72 years; 65% males; median follow-up, 1.7 years) were included. In comparison to placebo/control, use of aspirin (odds ratio [OR], 0.75 [95% CI, 0.60–0.95]), VKA (0.38 [0.29–0.49]), apixaban (0.31 [0.22–0.45]), dabigatran (0.29 [0.20–0.43]), edoxaban (0.38 [0.26–0.54]), rivaroxaban (0.27 [0.18–0.42]), and the Watchman device (0.36 [0.16–0.80]) significantly reduced the risk of any stroke or systemic embolism in nonvalvular AF patients, as well as all-cause mortality (aspirin: OR, 0.82 [0.68–0.99]; VKA: 0.69 [0.57–0.85]; apixaban: 0.62 [0.50–0.78]; dabigatran: 0.62 [0.50–0.78]; edoxaban: 0.62 [0.50–0.77]; rivaroxaban: 0.58 [0.44–0.77]; and the Watchman device: 0.47 [0.25–0.88]). Apixaban (0.89 [0.80–0.99]), dabigatran (0.90 [0.82–0.99]), and edoxaban (0.89 [0.82–0.96]) reduced risk of all-cause death as compared to VKA.

CONCLUSIONS The entire spectrum of therapy to prevent thromboembolism in nonvalvular AF significantly reduced stroke/systemic embolism events and mortality.

Comparative effectiveness of interventions for stroke prevention in atrial fibrillation: a network meta-analysis *J Am Heart Assoc* 2016;5:e003206, LG Tereshchenko, CA Henrikson, J Cigarroa, JS Steinberg

CHEST World Congress 2016

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CHEST world congress 2016 brought together pulmonary, critical care and sleep medicine clinicians from around the world to experience interactive hands-on simulation training, keynote addresses and presentations from leading healthcare experts on the latest research in chest medicine.

A gas-driven pump is used to deliver prostacyclin in patients with severe pulmonary hypertension and concomitant haematologic malignancy

An implantable gas driven infusion pump has been used to deliver treprostinil to patients with severe pulmonary hypertension and concomitant haematological malignancy.

Pulmonary hypertension is a progressive fatal disease requiring aggressive, specific therapy. Subcutaneous treprostinil is associated with local side effects and intravenous administration with external pumps with rare but severe catheter-related infections, explains Regina Steringer-Mascherbauer, MD, of KH Elisabethinen, Linz, Austria.

The availability of a gas driven implantable pump for intravenous treprostinil administration represents significant progress. This surgical approach requires careful interdisciplinary interaction, however, as patients with pulmonary hypertension carry significantly elevated anaesthesia risks, especially if they harbour relevant comorbidities.

> "With intensive cooperation between all departments involved and extensive experience with the implantation procedure, the pump can be safely offered, even to patients with severe haematologic comorbidities such as lymphoma.

Data were documented in the Elisabethinen Linz Pulmonary Hypertension Registry.

Between 2012 and 2015, three patients with severe pulmonary hypertension and concomitant haematological malignancy were implanted. According to standard operating procedures, all patients were uptitrated with subcutaneous treprostinil.

Eligibility for anaesthesia and pump implantation was independently assessed by the pulmonary hypertension specialist, anaesthesiologist, and surgeon. A dedicated surgical team performed all implantations. No perioperative complications were observed.

In the third patient, a postoperative bleeding episode was managed during a hospital stay. No other complications or infections were observed. The first patient died from the underlying malignancy 12 months after pump implantation.

A fourth patient, a 65-year-old female with post polycythemia vera myelofibrosis is on the waiting list for implantation because thrombocytopenia, a known side effect of ruxolitinib, is now a contraindication to surgery.

Dr Steringer-Mascherbauer concluded that the coincidence of life-threatening diseases presents an extraordinary challenge. With intensive cooperation between all departments involved and extensive experience with the implantation procedure, the pump can be safely offered, even to patients with severe haematologic comorbidities such as lymphoma.

The implantation of a gas driven pump for treprostinil therapy has not yet been reported in patients with severe haematologic comorbidity, and must be restricted to surgically experienced, specialised pulmonary hypertension centres. ■

"With intensive cooperation between all departments involved and extensive experience with the implantation procedure, the pump can be safely offered, even to patients with severe haematologic comorbidities such as lymphoma. >10

"Prior to inclusion in the study, 72 patients with sleep apnoea hypopnoea syndrome and 23 snoring subjects underwent polysomnography and echocardiography to evaluate their heart structure, haemodynamic parameters, and the presence or absence of pulmonary hypertension. >12

Long-term mechanical ventilation is effective adjunctive therapy for children with severe pulmonary hypertension

In children with severe lung disease and severe pulmonary hypertension, long-term mechanical ventilation has been shown to offer an effective clinical benefit as adjunctive therapy to vasodilator medications in those who, without such therapy, death is the likely outcome.

The mortality rate of infants with severe chronic lung disease and pulmonary hypertension remains very high at around 70%, despite the availability of multiple vasodilator agents which have greatly improved the survival of children with pulmonary hypertension, explains Paul H. Sammut, of the University of Nebraska Medical Centre, Omaha.

The effects of hypercarbia on pulmonary artery pressure have been shown to be variable, but most clinicians believe hypercarbia exerts a significant pulmonary vasoconstricting effect and negative effect on the vasodilating capability of other agents.

Mechanical ventilation is capable of improving the hypercarbia level in these patients and, therefore, the potential to reduce the severity of pulmonary hypertension. Very few clinical studies have addressed this topic and almost no reports can be found in the paediatric literature.

Dr Sammut described the outcomes of six children who underwent tracheostomy tube placement and long-term (7 months to 8 years) mechanical ventilation, in addition to multiple-agent vasodilator therapy. All fell into the category described above and almost certainly would have died without this therapy.

Three children had pulmonary hypoplasia due to congenital diaphragmatic hernias, two had bilateral hypoplasia due to other aetiologies, and one had severe multicystic lung disease with anomalous pulmonary arterial supply. All received mechanical ventilation soon after birth and a tracheostomy tube later on. Two underwent extracorporeal membrane oxygenation for a period early in their course.

None of the patients has died. Three children, age 8 years, 17 months, and 7 months, suffer from persistent, severe pulmonary hypertension (>2/3 systemic level) and remain ventilated but are active. One attends school, in fact.

The child with multicystic lungs remains ventilated but exhibits near-normal pulmonary artery pressure. One child has normal pulmonary artery pressure at baseline and enjoys many daytime hours off the ventilator.

The sixth child was decannulated at 33 months and is an active 4-year-old with normal pulmonary artery pressure.

Dr Sammut concluded that, in children with severe lung disease and severe pulmonary hypertension, long-term mechanical ventilation was shown to offer an effective clinical benefit as adjunctive therapy to vasodilator medications in those who, without such therapy, death is the likely outcome.

Long-term mechanical ventilation can offer the chance of possible resolution of pulmonary hypertension in some children with severe lung disease and, in those whose pulmonary hypertension will not improve, it helps maintain survival such that other interventions (such as lung transplantation) may be more successful than if tried in the neonatal period. ■

Gas-driven implantable pump proves successful for treprostinil administration to patients with pulmonary hypertension

In the first report on surgical interventions in a large cohort of pulmonary hypertension patients, an implanted pump delivering treprostinil has been proven effective.

In 2009, a gas-driven implantable infusion pump was introduced for intravenous delivery of treprostinil for patients with pulmonary hypertension. Since 2010, Dr Steringer-Mascherbauer's centre has acquired vast experience with this innovative treatment explains Regina Steringer-Mascherbauer, MD, of KH Elisabethinen, Linz, Austria.

"In this first report on surgical interventions in a large cohort of pulmonary hypertension patients, an implanted pump delivering treprostinil was proven effective. Needed interventions were performed without complications.

Parenteral treprostinil has been administered without the frequent local side effects of subcutaneous infusion, a major step forward. A fully implantable gas-driven pump system minimises the risk of rare but life-threatening line infections as compared to intravenous delivery with external pumps. Surgical intervention may be needed in cases of drug delivery issues.

More than 36 patients were implanted and followed between 2010 and 2015. Data were documented in the Elisabethinen Linz Pulmonary Hypertension Registry.

No intraoperative complications were observed.

During more than 63 patient-years of follow-up, only five surgical interventions were needed in four patients 2, 4 ,8, and 28 months after implantation.

Catheter kinking was managed with local anaesthesia, and the other surgical interventions required general anaesthesia. One pump had to be refixed at the fascia. In another patient, a possible catheter occlusion required replacement of a part of the implanted catheter.

In a second session, a catheter loop due to noncoaxial implantation required complete catheter replacement. One pump had to be replaced as substantial weight loss led to rotation of the pump, rendering refill nearly impossible. Despite a seroma that resolved without surgical intervention after pump replacement, no complications occurred.

Dr Steringer-Mascherbauer concluded that in this first report on surgical interventions in a large cohort of pulmonary hypertension patients, an implanted pump delivering treprostinil was proven effective. Needed interventions were performed without complications. Close patient monitoring at a specialised, pulmonary arterial hypertension expert centre is recommended in case of catheter-related possible occlusion alarm, to renew the complete catheter. Catheters or even pumps can be replaced safely if needed. ■

Balloon pulmonary angioplasty reduces mean pulmonary arterial pressure to ≤30 mmHg in patients with CTEPH

Balloon pulmonary angioplasty has been proven effective to reduce mean pulmonary artery pressure to <30 mmHg, and the duration from symptom onset and diastolic pulmonary arterial pressure were determining factors in this success.

Patients with chronic thromboembolic pulmonary hypertension with mean pulmonary arterial pressure ≤30 mmHg have been shown to have a better prognosis than those with mean pulmonary arterial pressure >30 mmHg, explains Akihiro Tsuji, MD, of the National Cerebral and Cardiovascular Centre, Suita, Osaka, Japan.

> "It is important to evaluate factors predictive of effectiveness before performing balloon pulmonary angioplasty.

Recently, balloon pulmonary angioplasty was developed as an alternative therapy for inoperable patients with chronic thromboembolic pulmonary hypertension. Dr Tsuji and colleagues set out to clarify predicting factors for attaining mean pulmonary arterial pressure ≤30 mmHg after balloon pulmonary angioplasty.

Between 2012 and 2014, 35 inoperable patients with chronic thromboembolic pulmonary hypertension qualified for the study. Clinical and haemodynamic data were collected and patients divided into two groups: 27 patients with mean pulmonary arterial pressure ≤30 mmHg and eight with mean pulmonary arterial pressure >30 mmHg. Parameters associated with attainment of mean pulmonary arterial pressure ≤30 mmHg were evaluated.

A total of 148 balloon pulmonary angioplasty sessions were performed in 35 patients, an average of 4.2 ± 1.4 sessions per patient, were performed to treat 569 lesions. No patients needed mechanical respiratory or circulatory support, and no deaths were reported during the balloon pulmonary angioplasty procedures.

Patients were followed for an average of 4.3 ± 2.4 months. In multivariate analysis, the duration from symptom onset and baseline diastolic pulmonary arterial pressure were the only factors predicting attainment of mean pulmonary artery pressure ≤30 mmHg.

Dr Tsuji concluded that balloon pulmonary angioplasty was effective in reducing mean pulmonary artery pressure to ≤30 mmHg. Duration from symptom onset and diastolic pulmonary arterial pressure were the determining factors in this reduction.

It is important to evaluate factors predictive of effectiveness before performing balloon pulmonary angioplasty. Such evaluation may lead to selection of appropriate therapy, such as balloon pulmonary angioplasty alone, medical therapy alone, or both. ■

The incidence of obstructive sleep apnoea hypopnoea syndrome correlates with that of pulmonary hypertension

More than half of a cohort of patients with pulmonary artery systolic pressure ≥40 mmHg, and these patients had more severe sleep apnoea hypopnoea syndrome.

Sleep apnoea hypopnoea syndrome is associated with cardiovascular complications, including pulmonary circulation and systemic circulation, explains J. Zhang, MD, of the General Hospital of Ningxia Medical University, Yinchuan, China. Dr Zhang and colleagues set out to evaluate the impact of sleep apnoea hypopnoea syndrome on pulmonary hypertension and right heart function.

Prior to inclusion in the study, 72 patients with sleep apnoea hypopnoea syndrome and 23 snoring subjects underwent polysomnography and echocardiography to evaluate their heart structure, haemodynamic parameters, and the presence or absence of pulmonary hypertension. Of the 72 patients with sleep apnoea hypopnoea syndrome detected by echocardiography, 28 (38.89%) were found to also suffer from pulmonary hypertension (pulmonary artery systolic pressure ≥40 mmHg).

Only four of the 23 snoring subjects (17.39%) had pulmonary hypertension. Significantly more patients with sleep apnoea hypopnoea syndrome had pulmonary hypertension than snoring subjects ($P < 0.05$).

Significantly more patients with pulmonary hypertension exhibited right cardiac structural impairment than those without pulmonary hypertension ($P < 0.05$ or < 0.01).

The degree of pulmonary hypertension and right heart structure/haemodynamic change in patients with sleep apnoea hypopnoea syndrome and pulmonary hypertension correlated well with the severity of sleep apnoea hypopnoea syndrome.

Dr Zhang concluded that the incidence of sleep apnoea hypopnoea syndrome with pulmonary hypertension was higher; and pulmonary hypertension severity and right heart structural impairment in patients with sleep apnoea hypopnoea syndrome correlated with the severity of obstructive sleep apnoea hypopnoea syndrome.

The findings are a reminder to pay attention to pulmonary hypertension detection in patients with sleep apnoea hypopnoea syndrome. ■

Inflammatory response may play a key role in COPD-related pulmonary hypertension

C-reactive protein and procalcitonin may play a very important role in the formation of chronic obstructive pulmonary disease-related pulmonary hypertension.

Investigators set out to explore the blood percentage of neutrophils, C-reactive protein, and procalcitonin in patients with chronic obstructive pulmonary disease with and without pulmonary hypertension, and to explore the significance of the inflammatory response in chronic obstructive pulmonary disease-related pulmonary hypertension, explains Jing-Cheng Dong, PhD, of Nanjing Chest Hospital, China.

From 2013 to 2015, 72 patients with acute exacerbation of chronic obstructive pulmonary disease were divided into those with and without pulmonary hypertension according to pulmonary artery systolic pressure >40 mmHg. Twenty healthy persons were selected as a control group at the same period.

The two groups with chronic obstructive pulmonary disease were screened for serum procalcitonin; C-reactive protein; white blood cell count; neutrophil classification; smoking status; and comorbidities such as heart failure, hypertension, and diabetes. To compare levels of blood neutrophil percentage, C-reactive protein and procalcitonin were measured before after treatment. Correlations between blood neutrophil percentage, C-reactive protein, and procalcitonin levels and pulmonary artery systolic pressure were then analysed.

> "Neutrophils, C-reactive protein, and procalcitonin were not only involved in the inflammation of airways and lung parenchyma, but also may play a very important role in chronic obstructive pulmonary disease-related pulmonary hypertension.

Compared with the control group before treatment, patients with chronic obstructive pulmonary disease and pulmonary hypertension exhibited a serum procalcitonin concentration of 0.24 ± 0.43 ng/mL Those without pulmonary hypertension exhibited a serum procalcitonin concentration of 0.08 ± 0.07 ng/mL (difference statistically significant).

Patients with chronic obstructive pulmonary disease and pulmonary hypertension demonstrated a serum C-reactive protein concentration of 23.78 ± 42.79 ng/mL. Those without pulmonary hypertension demonstrated a serum C-reactive protein concentration of 2.58 ± 2.10 ng/mL ($P < 0.05$).

Procalcitonin and C-reactive protein were positively correlated in patients with acute exacerbation of chronic obstructive pulmonary disease ($r = 0.63$, $P < 0.05$). No correlation was observed between lower counts of peripheral white blood cells and length of hospital stay.

After treatment, in patients with chronic obstructive pulmonary disease and pulmonary hypertension, serum procalcitonin concentration was 0.20 + 0.08 ng/mL. In patients with chronic obstructive pulmonary disease without pulmonary hypertension, serum procalcitonin concentration was 0.21 ± 0.15 ng/mL (difference not statistically significant).

Before treatment, patients with chronic obstructive pulmonary disease and pulmonary hypertension, serum C-reactive protein concentration was 25.31 ± 0.73 ng/mL. In those with chronic obstructive pulmonary disease without pulmonary hypertension, serum C-reactive protein concentration was 22.96 ± 0.96 ng/mL (difference not statistically significant).

Dr Dong concluded that neutrophils, C-reactive protein, and procalcitonin were not only involved in the inflammation of airways and lung parenchyma, but also may play a very important role in chronic obstructive pulmonary disease-related pulmonary hypertension. ■

JOURNAL SCAN

Blood pressure variability and cognitive decline

Hypertension

Take-home message

- The authors evaluated 976 adults prospectively to assess the association between blood pressure and cognitive decline. Results showed that visit-to-visit variability in systolic pressure was associated with a faster decline in cognitive function.
- Visit-to-visit variability in diastolic pressure was associated with a faster decline in cognitive function in those aged 55 to 64 years only.

Dr Ronald G Victor

Blood pressure (BP) is the most variable measurement in everyday outpatient medicine. In a given patient, BP varies from beat-to-beat, hour-to-hour, night and day, and with the normal ebb and flow of daily emotional and physical activities. It also varies from one medical office visit to the next.

While such visit-to-visit variability in BP could be secondary to intermittent medication non-compliance, it could also indicate a primary problem in vascular health. Professor Peter Rothwell and coworkers at the University of Oxford suggested that stiff arteriosclerotic conduit vessels could impair baroreceptor buffering of BP and respond to small changes in intravascular volume status with large increases and decreases in BP. In this issue of *Hypertension*, two observational studies add further support to Professor Rothwell's hypothesis.

In a retrospective analysis of the massive ALLHAT study (Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial), the authors found that patients with self-reported medication nonadherence were more likely to have higher visit-to-visit BP variability, which only partially explained the association of higher visit-to-visit BP variability with increased risk of major cardiovascular events. Self-reported medication nonadherence is very weakly associated with actual drug blood levels, which are far more accurate.

In the second study, using observational data from the China Health and Nutrition Survey conducted between 1997 and 2004, the authors found that patients with high visit-to-visit BP variability had a higher risk of cognitive decline. Again, the association was independent of average BP.

While BP variability certainly is an important topic, this work will not impact clinical practice without randomised controlled trials to find the optimal drug regimens that affect 24-hour BP variability rather than clinic BP variability in such a way as to minimise the risk of major cardiovascular events from hypertension.

Abstract

The association between visit-to-visit variability of blood pressure (BP) and cognitive decline over time remains incompletely understood in a general population of older adults. We assessed the hypothesis that higher visit-to-visit variability in BP, but not mean BP, would be associated with faster decline in cognitive function among community-dwelling older adults. This prospective cohort study comprised 976 adults who had 3 or 4 visits with BP measurements as part of the China Health and Nutrition Survey from 1991, up to their first cognitive tests, and completed cognitive screening tests at ≥2 visits in 1997, 2000, or 2004. Visit-to-visit BP variability was expressed as the SD, coefficient of variation, or as the variation independent of mean BP across visits conducted at a mean interval of 3.2 years. Mean (SD) age at the first cognitive test was 64 (6) years. Using multivariable-adjusted linear mixed-effects models, we found higher visit-to-visit variability in systolic BP, but not mean systolic BP, was associated with a faster decline of cognitive function (adjusted mean difference [95% confidence interval] for high versus low tertile of SD variability: standardised composite scores -0.038 standard units (SU)/y [-0.066 to -0.009] and verbal memory -0.041 SU/y [-0.075 to -0.008]). Higher visit-to-visit variability in diastolic BP was associated with a faster decline of cognitive function, independent of mean diastolic BP, among adults aged 55 to 64 years but not those ≥65 years. Our results suggest that higher long-term BP visit-to-visit variability is associated with a faster rate of cognitive decline among older adults.

Visit-to-visit variability in blood pressure is related to late-life cognitive decline *Hypertension* 2016; [EPub ahead of print], B Qin, AJ Viera, P Muntner, et al.

JOURNAL SCAN

Trends in hypertension management and mortality among octogenarians

Hypertension

Take-home message

- This study evaluated data from a longitudinal study of octogenarians to better understand the relationship among hypertension, treatment of hypertension, and mortality in this age group compared with that in younger adults (50–79 years). Prevalence of hypertension in the study group was 40%, with an approximate 90% rate of treatment and target blood pressure of <150/90 mmHg achieved in 59% of patients. Highest all-cause mortality was associated with the lowest SBP (<110 mmHg); lowest all-cause mortality was associated with SBP 140 to 149 mmHg and 160 to 169 mmHg.
- The study results revealed a trend toward increased hypertension treatment in octogenarians but also suggest that stringent control of hypertension is not associated with improved mortality.

ABSTRACT The role of hypertension management among octogenarians is controversial. In this long-term follow-up (>10 years) study, we estimated trends in hypertension prevalence, awareness, treatment, and control among octogenarians, and evaluated the relationship of systolic blood pressure (SBP) ranges with mortality. Data were based on the English Longitudinal Study of Ageing (ELSA). Outcome measures were hypertension prevalence, awareness, treatment and control, and cardiovascular disease, and all-cause mortality events. Participants were separated into 8 categories of SBP values (<110, 110–119, 120–129, 130–139, 140–149, 150–159, 160–169, and >169 mmHg). Among 2692 octogenarians, mean SBP levels declined from 147 mmHg in 1998/2000 to 134 mmHg in 2012/2013. The decline was of lower magnitude in the 50 to 79 years old subgroup (n=22007). Hypertension prevalence and awareness were 40% and 13%, respectively, higher among octogenarians than the 50 to 79 years of age subgroup, but hypertension treatment rates were similar (≈90%). Around 47% of the treated octogenarians achieved conventional BP targets (<140/90 mmHg), increasing to 59% when assessed against revised targets (<150/90 mmHg). All-cause mortality rates were higher (hazard ratio, 1.55; 95% confidence interval, 0.89–2.72) at lower extremes of SBP values (<110 mmHg). The lowest cardiovascular disease and all-cause mortality risk among treated octogenarians was observed for an SBP range of 140 to 149 mmHg (1.04, 0.60–1.78) and 160 to 169 mmHg (0.78, 0.51–1.21). An increasing trend in hypertension awareness and treatment was observed in a large sample of community-dwelling octogenarians. The results do not support the view that more stringent BP targets may be associated with lower mortality.

Longitudinal trends in hypertension management and mortality among octogenarians: prospective cohort study. *Hypertension* 2016; [EPub ahead of print], A Dregan, R Ravindrarajah, N Hazra, et al.

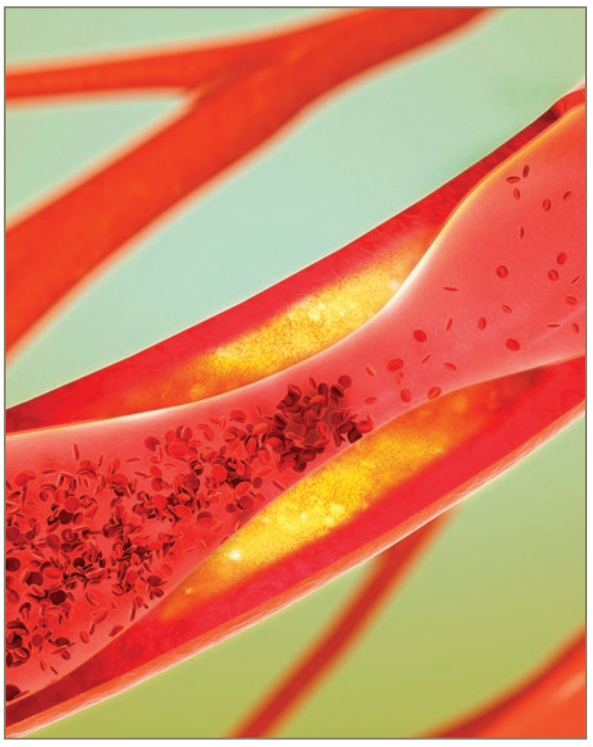
JOURNAL SCAN

Statin therapy improves outcomes in patients with coronary spasm

Journal of the American Heart Association

Take-home message

- In a retrospective study, the data of 640 patients with vasospastic angina who had no evidence of significant coronary artery stenosis were examined. Patients were followed for up to 12 years. Patients who were taking statins on admission had a 95.2% rate of dyslipidaemia compared with 26.5% of patients who were not taking statins on admission. Statin therapy was shown to be negatively associated with the primary endpoint of major cardiac events (MACE), including cardiac death, nonfatal myocardial infarction, and unstable angina (HR, 0.11; P = 0.033). Patients in the statin group also had a better 5-year survival without MACE (100% vs 91.7%; P = 0.002).
- Use of statin therapy, independent of level of dyslipidaemia control, was associated with a lower rate of MACE and improved prognosis in patients with vasospastic angina and no evidence of obstructive coronary artery disease.



BACKGROUND Statin therapy reduces the risk of cardiovascular events in patients with obstructive coronary artery disease. The aim of the present study was to determine the effects of statins on the prognosis of patients with coronary vasospastic angina (VSA) free of significant atherosclerotic stenosis.

METHODS AND RESULTS After exclusion of 475 from 1877 consecutive patients who underwent an acetylcholine-provocation test between January 1991 and December 2010, data of 640 VSA patients without significant organic stenosis of the remaining 1402 were analysed retrospectively. Propensity score matching was performed to reduce the effect of treatment-selection bias and possible confounders. The primary endpoint was major adverse cardiac events (MACE), including cardiac death, nonfatal myocardial infarction, and unstable angina. Among the study population, dyslipidaemia on admission was identified in 160 of 168 (95.2%) patients of the statin group compared with only 125 of 472 (26.5%) of the no-statin group. Of the 640 patients, 24 (3.8%) developed MACE. Multivariate Cox hazard regression analysis identified statin therapy as a significant negative predictor of MACE (hazard ratio, 0.11; 95% CI, 0.02-0.84; P = 0.033). In the propensity-score matched cohorts (n=128 each), Kaplan-Meier survival curve showed a better 5-year MACE-free survival rate for patients of the statin group compared to the no-statin group (100% vs 91.7%, respectively; P = 0.002).

CONCLUSIONS Statin therapy correlated with a lower rate of cardiovascular events in VSA patients free of significant organic stenosis. Statins seems to improve the prognosis of VSA patients free of significant organic stenosis.

Impact of statin therapy on clinical outcome in patients with coronary spasm. *J Am Heart Assoc* 2016;5(5):e003426, M Ishii, K Kaikita, K Sato, et al.

JOURNAL SCAN

2016 European guidelines on cardiovascular disease prevention

European Heart Journal

Take-home message

- The Sixth European Joint Task Force is responsible for the 2016 guidelines, an evidence-based consensus on cardiovascular disease (CVD) prevention. The authors emphasise that CVD prevention is a coordinated set of actions, for both individuals and populations. Preventive measures to curtail smoking lower the rates of coronary artery disease. Other risk factors covered include physical activity, nutrition, body weight, and many associated conditions such as diabetes and hypertension. Current treatment options are described for CVD and associated diseases. Although outcomes continue to improve, CVD still ranks high as a cause of morbidity and mortality.
- The 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice is not only a comprehensive set of guidelines but a thorough review of CVD, risk factors, and remaining gaps in knowledge.

ABSTRACT Cardiovascular disease (CVD) prevention is defined as a coordinated set of actions, at the population level or targeted at an individual, that are aimed at eliminating or minimising the impact of CVDs and their related disabilities. CVD remains a leading cause of morbidity and mortality, despite improvements in outcomes. Age-adjusted coronary artery disease (CAD) mortality has declined since the 1980s, particularly in high-income regions. CAD rates are now less than half what they were in the early 1980s in many countries in Europe, due to preventive measures including the success of smoking legislation. However, inequalities between countries persist and many risk factors, particularly obesity and diabetes mellitus (DM), have been increasing substantially.

2016 European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016;[EPub Ahead of Print], MF Piepoli, AW Hoes, S Agewall, et al.

NEWS

Death and stroke rates are equivalent for surgery and TAVR at 2 years

Intermediate-risk patients with severe aortic stenosis who receive minimally invasive transcatheter aortic valve replacement (TAVR) experience similar rates of death and disabling strokes after 2 years as those undergoing standard open heart surgical replacement.

This outcome of the randomised, controlled Placement of AoRtic TraNscathetER Valves (PARTNER) 2A noninferiority trial – the first to evaluate TAVR in patients considered at intermediate risk – suggests that TAVR is at least as safe and effective as surgery in these patients. Results were presented at the American College of Cardiology's 65th Annual Scientific Session.

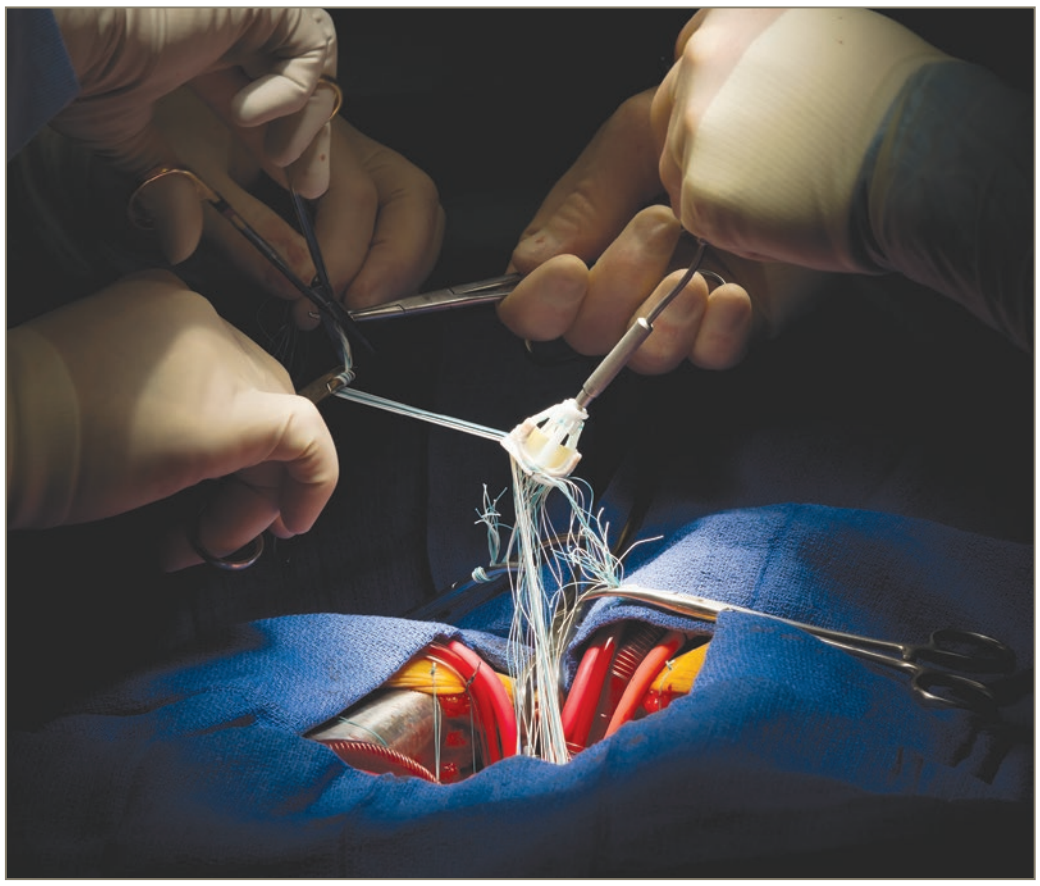
Patients receiving TAVR also experienced shorter hospital stays and a lower incidence of some major complications than those undergoing surgery.

Martin B. Leon, MD, of New York Presbyterian Medical Centre and coprincipal investigator of the PARTNER trials, explained that roughly one in five patients undergoing surgical aortic valve replacement in the US are at intermediate risk; so intermediate- and high-risk patients comprise the top quartile of patients needing an aortic valve replacement.

He said, "For the past 5 years, TAVR has been growing in use and acceptance largely based on clinical evidence from multiple randomised controlled trials. These have been limited to patients at the highest risk for surgery, however. We have demonstrated that death and stroke are equivalent in these patients and may be fewer in the transfemoral group."

Outcomes using the Sapien XT valve were compared with open heart surgery valve replacement among 2032 intermediate-risk patients treated between 2011 and 2013 at 57 sites, all but two in the US. Patients were randomly assigned to TAVR (n=1011) or surgery (n=1021). Of those in the TAVR group, 76% underwent transfemoral placement, and the rest, transthoracic placement in which the new valve was threaded through a cut in the chest wall.

Results in meeting the primary endpoint of all-cause death and disabling strokes were comparable at 2 years: 19.3% for TAVR and 21.1% for surgery. Among TAVR patients with transfemoral placement of the valve, the combined rate of death and disabling stroke was lower, 16.8% for TAVR vs 20.4% for surgery (P = 0.05).



"When we compared transthoracic TAVR patients to those having surgery, they were about the same. The transfemoral group clearly experienced lower rates of death and strokes," Dr Leon said.

The researchers also found significant differences in the secondary clinical endpoints of hospital stay, valve function, and major complications. Some favoured TAVR, some surgery. For example, TAVR patients spent less time in the hospital. Average time in the intensive care unit was 2 days with TAVR vs 4 days with surgery, and average hospitalisation for TAVR was 6 days vs 9 days with surgery. TAVR also appeared to improve aortic valve areas more than surgery, meaning that the valve performed better as measured by echocardiography through 2 years.

TAVR also yielded significantly lower rates of acute kidney injury, severe bleeding events, and new-onset atrial fibrillation than surgery. The surgery group, on the other hand, experienced fewer major vascular complications and paravalvular regurgitation.

"Two-year follow-up allowed enough time to accurately assess the relative performance of these two valve replacement therapies. He added, adding that he suspects the findings will potentially affect future clinical TAVR guidelines," Dr Leon said.

"We know surgery is good, but it is a major procedure and for many patients, a less invasive approach may be preferable. As we continue to evolve the procedure and technology, it's important to know whether TAVR is an effective alternative in these lower-risk patients," he said. ■

JOURNAL SCAN

Increased incidence of ventricular arrhythmias in patients with advanced cancer and ICDs

Journal of the American College of Cardiology: Clinical Electrophysiology

Take-home message

- This is a retrospective study in which patients with an implantable cardioverter-defibrillator (ICD) and cancer diagnosis were followed from January 2007 to June 2015 for incidence of ventricular fibrillation (VF) or ventricular tachycardia (VT). At the time of ICD placement, 209 of 1598 patients (13.1%) had a known cancer diagnosis. In 102 patients (6.4%), cancer diagnosis was made after the ICD was placed. In 23.2 ± 23.6 months of follow-up after cancer diagnosis, 32% of patients had at least one episode of VF or VT. VF/VT events per month were significantly higher after cancer diagnosis (1.19 ± 0.32 vs 0.12 ± 0.21; P = 0.03) and increased in patients with stage IV cancer compared with earlier stages (P = 0.03), with the incidence of VT/VF reported at 41.2% in this group.
- Ventricular arrhythmias occur in 32% of patients with an ICD after a diagnosis of cancer, with the incidence increasing to 41.2% in end-stage cancer. The issue of ICD management should be addressed in discussions about end-of-life care when applicable.

Abstract

OBJECTIVES This study evaluated the incidence of ventricular arrhythmia and implantable cardioverter-defibrillators (ICDs) therapies in patients with a diagnosis of cancer.

BACKGROUND Cardiac disease and cancer are prevalent conditions and share common predisposing factors. No studies have assessed the impact of cancer on the burden of ventricular arrhythmia in patients with cancer and ICDs.

METHODS Retrospective study of patients with an ICD and cancer followed from January 2007 to June 2015. Rates of ventricular tachycardia (VT) and ventricular fibrillation (VF) before and after patients' cancers were diagnosed were evaluated by searching device data collection systems. Rates were adjusted for length of follow-up and compared using the Wilcoxon test, and times to first therapy following diagnosis (stages I to III vs IV) were compared using Kaplan-Meier curves and log-rank test.

RESULTS Among 1598 patients with an ICD, 209 patients (13.1%) had a pathological diagnosis of malignancy; and in 102 patients (6.4%), malignancy was diagnosed following device insertion. After the diagnosis of cancer, 32% of patients experienced VT/VF over 23.2 ± 23.6 months, and the frequency of arrhythmic events was significantly increased after the diagnosis (1.19 ± 0.32 vs 0.12 ± 0.21 episodes per month, respectively; P = 0.03). The incidence of VT/VF was markedly higher in patients with stage IV cancer than in those with earlier stages (P = 0.03). In this group, the incidence of VT/VF was 41.2%, with an average of 7.2 ± 18.5 events per patient, all of whom received ICD shocks. The rate of ICD deactivation in stage IV patients was 35.3%. Inappropriate therapies occurred in 13.7%, and atrial fibrillation was the most frequent cause.

CONCLUSIONS One-third of patients who had received ICDs developed ventricular arrhythmia after a diagnosis of cancer. The incidence was significantly higher in those with advanced metastatic disease. Findings underscore the need to discuss ICD management as part of end-of-life care.

Increased Incidence of Ventricular Arrhythmias in Patients With Advanced Cancer and Implantable Cardioverter-Defibrillators *JACC Clin Electrophysiol* 2016 May 18; [EPub Ahead of Print], A Enriquez, J Biagi, D Redfearn, et al.

JOURNAL SCAN

Predictors and risk of ventricular tachyarrhythmias or death in black and white cardiac patients

Journal of the American College of Cardiology: Clinical Electrophysiology

Take-home message

- The authors studied ethnic differences and predictors of ventricular tachyarrhythmias (VTA) in 1777 patients (n = 139 black; n = 1638 white) implanted with ICDs or combined defibrillator and CRT (CRT-D). After 4 years of follow-up, multivariate analysis showed that blacks compared with whites had a higher risk of VTA or death (HR, 1.6; P = 0.002) and a higher risk of VTA alone (HR, 1.71; P = 0.002); this was consistent in both ICD and CRT-D groups. Increased systolic blood pressure and larger cardiac volume were independent risk factors for VTA in blacks.
- Blacks compared with whites had a higher risk of VTA and death in both ICD and CRT-D groups.

OBJECTIVES The study sought to analyse the risk of ventricular tachyarrhythmia (VTA) or death in black and white subjects implanted with implantable cardioverter-defibrillators (ICDs) or defibrillator and combined cardiac resynchronization therapy (CRT-D) in the MADIT-CRT (Multicentre Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy) trial.

BACKGROUND There are limited data on ethnic differences in the risk for VTA in mildly symptomatic heart failure patients with left ventricular dysfunction.

METHODS The risk for first VTA (≥180 beats/min) or death was evaluated in black (n = 139) versus white (n = 1638) patients enrolled in the MADIT-CRT trial using Kaplan-Meier survival analyses and Cox proportional hazards regression models after adjustment for relevant clinical covariates. Multivariate analysis was used to identify race-specific risk factors for VTA.

RESULTS At 4 years of follow-up, the cumulative probability for a first VTA or death was significantly higher among black patients (42%) as compared with whites (34%; log-rank P value for the overall difference during follow-up = 0.01). Multivariate analysis confirmed significantly higher risk of VTA or death (hazard ratio: 1.60; 95% confidence interval: 1.18 to 2.17; P = 0.002), and higher risk of VTA alone (hazard ratio: 1.71; 95% confidence interval: 1.22 to 2.41; P = 0.002) in blacks compared to whites. The findings were similar in both ICD and CRT-D implanted patients, with no significant race-to-treatment-interaction (interaction P > 0.05). Independent risk factors for VTA among blacks included increased systolic blood pressure values and larger cardiac volumes.

CONCLUSIONS In the MADIT-CRT trial, black patients had a significantly higher rate of ventricular tachyarrhythmias or death compared to whites, with either an implanted ICD or CRT-D.

Predictors and risk of ventricular tachyarrhythmias or death in black and white cardiac patients: an MADIT-CRT trial substudy. *JACC Clin Electrophysiol* 2016 May 18; [EPub Ahead of Print], A Sabbag, I Goldenberg, AJ Moss, et al.

EXPERT OPINION

Top abstracts from ACC 2016

RECOMMENDATIONS BY DR BEN SCIRICA

Session 401 – Opening showcase and the joint ACC/JACC late-breaking clinical trials featuring the Simon Dack lecture

401-17 – Blood pressure lowering in people at moderate risk. The HOPE-3 trial. *EM Lonn.*

Take-home message

- In the HOPE-3 trial, researchers randomised 12,705 patients with moderate cardiovascular risk to evaluate candesartan/hydrochlorothiazide vs placebo for the primary prevention of cardiovascular events. In patients receiving candesartan/hydrochlorothiazide, there was a greater decrease in blood pressure (6.0/3.0 mmHg) than in the placebo group. At baseline, mean blood pressure was 138.1/18.9 mmHg. The rate of cardiovascular death and events was significantly lower among patients with a systolic blood pressure >143.5 mmHg receiving active treatment. Overall, the rate of cardiovascular death and events were similar between groups.
- In patients with an intermediate risk for cardiovascular disease, researchers concluded that lowering blood pressure with candesartan/hydrochlorothiazide was not associated with fewer major cardiovascular events than placebo.

401-18 – Effects of rosuvastatin on cardiovascular disease in moderate risk primary prevention in diverse ethnic groups. *J Bosch.*

Take-home message

- In the HOPE-3 trial, researchers randomised 12,705 patients with moderate risk for cardiovascular disease to evaluate rosuvastatin vs placebo for the primary prevention of cardiovascular events. In patients receiving rosuvastatin, there was a greater decrease in LDL (26.5%) than in patients receiving placebo. Rosuvastatin was also associated with fewer cardiovascular deaths and events than placebo (P = 0.002 and P < 0.001, respectively). Muscle symptoms were more common in the rosuvastatin group.
- In patients with an intermediate risk for cardiovascular disease, researchers concluded that rosuvastatin was associated with fewer major cardiovascular events than placebo.

401-19 – Effects of combined lipid and BP-lowering on cardiovascular disease in a moderate risk global primary prevention population. *S Yusuf.*

Take-home message

- In the HOPE-3 trial, researchers randomised 12,705 patients with moderate risk for cardiovascular disease to receive candesartan/hydrochlorothiazide, rosuvastatin, or placebo in combination or alone. In patients receiving combined blood pressure and lipid-lowering therapy, there was a greater decrease in LDL (33.7 mg/dL) and a greater decrease in systolic blood pressure (6.2 mmHg) than in patients receiving dual placebo. The combined-therapy group also had a significantly lower rates of cardiovascular death and events (P = 0.005 and P = 0.003, respectively). Adverse events associated with combined therapy included muscle weakness and dizziness.
- In patients with an intermediate risk for cardiovascular disease, researchers concluded that combined blood pressure and lipid-lowering therapy is associated with fewer cardiovascular events than placebo.

Session 404 – Joint American College of Cardiology/*Journal of the American Medical Association* late-breaking clinical trials

404-08 – Impact of the cholesteryl ester transfer protein inhibitor evacetrapib on cardiovascular events: results of the ACCELERATE trial. *SJ Nicholls, A Lincoff, P Barter, et al.*

Take-home message

- In the ACCELERATE trial, researchers randomised 12,092 patients with high-risk vascular disease to receive evacetrapib or placebo in addition to standard treatment. The trial was prematurely terminated due to clinical futility. No major safety concerns were observed.
- Researchers concluded that the addition of evacetrapib to standard treatment does not improve cardiovascular outcomes in patients with high-risk vascular disease.

404-12 – Low-density lipoprotein cholesterol, familial hypercholesterolemia mutation status and risk for coronary artery disease. *AV Khera, H-H Won, GM Peloso, et al.*

Take-home message

- It is often thought that patients with severe hypercholesterolaemia have familial hypercholesterolaemia; therefore, researchers evaluated the presence of the familial hypercholesterolaemia (FH) mutation in patients with and without coronary artery disease (CAD). In patients without CAD and LDL ≥190 mg/dL, 1.9% carried a FH mutation; in patients with CAD and LDL ≥190 mg/dL, 1.8% carried a FH mutation. Researchers also found that patients with LDL ≥190 mg/dL who carried a FH mutation had a 22-fold higher risk for CAD than patients with LDL ≥190 mg/dL who did not carry a FH mutation.
- A small number of patients with severe hypercholesterolemia carry a FH mutation, which is associated with a significantly higher risk for CAD.

Session 405 – Joint American College of Cardiology/TCT late-breaking clinical trials

405-12 – Effect of early administration of intravenous beta blockers in patients with ST-elevation myocardial infarction before primary percutaneous coronary intervention. The early-BAMI trial. *V Roolvink, B Ibanez, JP Ottervanger, et al.*

Take-home message

- The use of beta blockers before primary percutaneous coronary intervention (PCI) is not well studied; therefore, in the Early-BAMI trial, researchers randomised 683 patients with ST-segment elevation myocardial infarction (STEMI) to receive intravenous metoprolol or placebo before PCI. The mean age was 62 years, and majority of patients were male (75%). Researchers did not find a significant difference in infarct size between the groups or in the rate of adverse events. The metoprolol group had a lower incidence of malignant arrhythmias than the placebo group (3.6% vs 6.9%, respectively; P = 0.05).
- Metoprolol administered before primary PCI did not reduce infarct size when compared with placebo among patients with STEMI.

Session 410 – Joint American College of Cardiology/*New England Journal of Medicine* late-breaking clinical trials

410-08 – Antiarrhythmic drugs for shock-refractory out-of-hospital cardiac arrest: the resuscitation outcomes consortium amiodarone, lidocaine or placebo study. *PJ Kudenchuk.*

Take-home message

- In patients with out-of-hospital cardiac arrest (OHCA), antiarrhythmic drugs are often used for shock-refractory ventricular fibrillation or pulseless ventricular tachycardia, even though there is no proven survival benefit. Researchers randomised 3027 patients with shock-refractory ventricular fibrillation or pulseless ventricular tachycardia OHCA to receive standard care along with amiodarone, lidocaine, or placebo. They did not find differences in survival or neurologic outcome between the groups.
- Researchers concluded that survival and neurologic outcomes were not improved with amiodarone or lidocaine when compared with placebo for OHCA due to initial shock-refractory ventricular fibrillation or pulseless ventricular tachycardia.

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JOURNAL SCAN

Impact of post-PCI fractional flow reserve on clinical decision-making and long-term outcomes

JACC: Cardiovascular interventions

Take-home message

- The authors evaluated data from 574 consecutive patients who underwent PCI and in whom pre- and post-PCI fractional flow reserve (FFR) was measured. Patients were followed for 31 ± 16 months. PCI was associated with a significant improvement in FFR (P < 0.0001). Post-PCI FFR measurement identified 143 lesions (21%) in the ischaemic range (≤0.81) that were initially thought to be acceptable by angiography alone. FFR >0.86 was associated with a significant decrease in major adverse cardiovascular events compared with FFR ≤0.86 (17% vs 23%; log-rank P = 0.02).
- FFR >0.86 is associated with improved outcomes after PCI, and measurement of post-PCI FFR increases identification of clinically significant lesions not seen on angiography.

OBJECTIVES This study sought to evaluate the impact of fractional flow reserve (FFR) after percutaneous coronary intervention (PCI) on subsequent in-lab interventional management vessels that had undergone pre-PCI FFR and its prognostic value in predicting long-term (>1 year) outcomes.

BACKGROUND Post-PCI FFR has been shown to be a predictor of intermediate-term (6 months) adverse events. However, its impact on immediate post procedure clinical decision making and long-term outcomes is not known.

METHODS Consecutive patients undergoing PCI who had pre- and post-PCI FFR evaluations were followed for major adverse cardiovascular events (MACE).

RESULTS In the study 574 patients (664 lesions) were followed for 31 ± 16 months. PCI led to significant improvement in FFR from 0.65 ± 0.14 to 0.87 ± 0.08 (P < 0.0001). Despite satisfactory angiographic appearance, 143 lesions (21%) demonstrated post-PCI FFR in the ischaemic range (FFR ≤0.81). After subsequent interventions, FFR in this subgroup increased from 0.78 ± 0.08 to 0.87 ± 0.06 (P < 0.0001). Final FFR cutoff of ≤0.86 had the best predictive accuracy for MACE and ≤0.85 for TVR. Patients who achieved final FFR >0.86 had significantly lower MACE compared to the final FFR ≤0.86 group (17% vs 23%; log-rank P = 0.02). Final FFR ≤0.86 had incremental prognostic value over clinical and angiographic variables for MACE prediction.

CONCLUSIONS Post-PCI FFR reclassified 20% of angiographically satisfactory lesions, which required further intervention thereby providing an opportunity for complete functional optimisation at the time of the index procedure. This is particularly important as FFR post-PCI FFR was a powerful independent predictor of long-term outcomes.

Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes *JACC Cardiovasc Interv* 2016;9(10):1022–1031, SK Agarwal, S Kasula, Y Hacioglu, et al.

JOURNAL SCAN

Long-term benefit of guideline-based treatment in acute myocardial infarction

Journal of the American College of Cardiology

Take-home message

- The long-term benefit (17 years) of five guideline-based therapies for acute myocardial infarction was evaluated; therapies included aspirin, beta blockers, acute reperfusion therapy, door-to-balloon (D2B) time ≤90 minutes, and door-to-needle (D2N) time to fibrinolysis ≤30 minutes. Patients who received aspirin, beta blockers, and acute reperfusion therapy on presentation lived longer than those patients who did not: 0.78 (SE, 0.05), 0.55 (SE, 0.06), and 1.03 (SE, 0.12) years, respectively. Patients with D2B and D2N times within the recommended time cut-offs had a life expectancy of 1.08 (SE, 0.49) and 0.55 (SE, 0.12) years longer than their counterparts who received therapy outside those parameters.
- Not only does guideline-based therapy for acute myocardial infarction improve 30-day survival, it also results in a sustained benefit in survival that can be observed as far out as 17 years.

BACKGROUND Guideline-based admission therapies for acute myocardial infarction (AMI) significantly improve 30-day survival, but little is known about their association with long-term outcomes.

OBJECTIVES This study evaluated the association of 5 AMI admission therapies (aspirin, beta-blockers, acute reperfusion therapy, door-to-balloon [D2B] time ≤90 min, and time to fibrinolysis ≤30 min) with life expectancy and years of life saved after AMI.

METHODS We analysed data from the Cooperative Cardiovascular Project, a study of US Medicare beneficiaries hospitalised for AMI, with 17 years of follow-up. Life expectancy and years of life saved after AMI were calculated using Cox proportional hazards regression with extrapolation using exponential models.

RESULTS Survival for recipients and non-recipients of the 5 guideline-based therapies diverged early after admission and continued to diverge during 17-year follow-up. Receipt of aspirin, beta-blockers, and acute reperfusion therapy on admission was associated with longer life expectancy of 0.78 (standard error [SE]: 0.05), 0.55 (SE: 0.06), and 1.03 (SE: 0.12) years, respectively. Patients receiving primary percutaneous coronary intervention (PCI) within 90 min lived 1.08 (SE: 0.49) years longer than patients with D2B times >90 min, and door-to-needle (D2N) times ≤30 min were associated with 0.55 (SE: 0.12) more years of life. A dose-response relationship was observed between longer D2B and D2N times and shorter life expectancy after AMI.

CONCLUSIONS Guideline-based therapy for AMI admission is associated with both early and late survival benefits, and results in meaningful gains in life expectancy and large numbers of years of life saved in elderly patients.

Association of Guideline-Based Admission Treatments and Life Expectancy After Myocardial Infarction in Elderly Medicare Beneficiaries *J Am Coll Cardiol* 2016;67:2378_2391, EM Bucholz, NM Butala, SL Normand, Y Wang, HM Krumholz.

Confidence from Evidence and Real World Experience*

*Xarelto has evidence for its efficacy and safety profile for eligible patients from RCTs and real world studies in SPAF[1-3] and PE/DVT.[4,5] Xarelto is the world's most prescribed NOAC,[6] with over 18 million patients treated across multiple indications.[7,8]

RCT=randomised controlled trial; SPAF=stroke prevention in atrial fibrillation; PE=pulmonary embolism; DVT=deep vein thrombosis; NOAC=non-vitamin K antagonist oral anticoagulant.
Calculation based on IMS Health MIDAS, Database: Monthly Sales December 2015.

PBS Information: Authority Required (STREAMLINED). Refer to PBS Schedule for full authority information.

PLEASE REVIEW THE FULL PRODUCT INFORMATION (PI) BEFORE PRESCRIBING. APPROVED PI AVAILABLE AT WWW. BAYERRESOURCES.COM.AU/RESOURCES/UPLOADS/PI/FILE9466.PDF OR UPON REQUEST FROM BAYER AUSTRALIA LTD.

Minimum Product Information. XARELTO® (rivaroxaban) INDICATIONS: Prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks); 10 mg tablet once daily. Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke; 20 mg tablet once daily (15 mg for patients with CrCl 30-49 mL/min). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and pulmonary embolism (PE); 15 mg tablet twice daily for 3 weeks, followed by 20 mg tablet once daily. Xarelto 15 mg and 20 mg tablets should be taken with food. Tablets may be crushed and administered orally (mixed with water or applesauce) or given through gastric tubes. See full PI for details. **CONTRAINDICATIONS:** Hypersensitivity to rivaroxaban or to any of the excipients, clinically significant active bleeding, lesions at increased risk of clinically significant bleeding and patients with spontaneous impairment of haemostasis, significant hepatic disease which is associated with coagulopathy, dialysis or severe renal impairment with a creatinine clearance < 15 mL/min for Xarelto 10 mg or < 30 mL/min for Xarelto 15 mg and 20 mg, concomitant treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein, Pregnancy, Lactation. **PRECAUTIONS:** Increased bleeding risk such as general haemorrhagic risk (see PI for list), bronchiectasis or history of pulmonary bleeding, renal impairment, hepatic impairment, surgery and interventions, spinal/epidural anaesthesia or puncture, patients with prosthetic valves (no clinical data), haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy, lactose intolerance. **INTERACTIONS WITH OTHER MEDICINES:** Care to be taken if concomitantly used with medicines affecting haemostasis; concomitant administration with NSAIDs, platelet aggregation inhibitors, other anticoagulants. **ADVERSE EFFECTS:** Please refer to PI for a complete list. Very common and common adverse reactions ($\geq 1\%$) include post procedural haemorrhage, increased transaminases, gingival bleeding, constipation, diarrhoea, nausea, pyrexia, oedema peripheral, contusion, pain in extremity, headache, dizziness, haematuria, menorrhagia, epistaxis, haematoma, anaemia, rectal haemorrhage, fatigue and ecchymosis, haemoptysis, pruritus, conjunctival haemorrhage, abdominal pain, dyspepsia, gastrointestinal haemorrhage, syncope, hypotension, increased gamma-glutamyltransferase, tachycardia, vomiting, asthenia, wound haemorrhage, subcutaneous haematoma and rash. Less frequent but serious adverse reactions include: urticaria, hypersensitivity, hyperglycaemia, cerebral, cerebellar and intracranial haemorrhage, haemorrhagic transformation stroke, jaundice, eye haemorrhage, loss of consciousness, angioedema, allergic oedema, cholestasis, hepatitis and thrombocytopaenia. **DOSAGE AND ADMINISTRATION:** see INDICATIONS above. **BASED ON PI DATED:** 09 Nov 2015.

References: 1. Patel MR *et al. N Engl J Med* 2011;365:883–91. **2.** Camm J *et al. Eur Heart J.* 2015 Sep 1. pii: ehv466. [Epub ahead of print]. **3.** Tamayo S *et al. Clin Cardiol* 2015;38:63–8. **4.** Prins MH *et al. Thrombosis J* 2013;11(1):21. **5.** Beyer-Westendorf J *et al. Blood* 2014;124:955–62. **6.** IMS Health MIDAS, Database: Monthly Sales June 2015. **7.** Calculation based on IMS Health MIDAS, Database: Monthly Sales December 2015. **8.** Xarelto® (rivaroxaban) Product Information, 9 November 2015.

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